## SECTION 5.0
## XIENCE V EVEROLIMUS ELUTING CORONARY STENT SYSTEM DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) is a combination product comprised of a device (stent system) and a drug coating (everolimus in a polymer coating). The XIENCE V EECSS was designed to meet several key performance objectives. The FDA approved and proven MUTLI-LINK VISION® and MULTI-LINK MINI VISION® Coronary Stent Systems were chosen because these systems offered a flexible stent with thin struts and excellent deliverability. A thin, biocompatibility drug coating was also very important. The drug coating components were chosen because these materials were efficacious with reduced drug loading, stable polymers, offered robust coating integrity, and were shown to be both hemocompatible and compatible with coronary vasculature.

The XIENCE V RX EECSS consists of the coated L-605 Cobalt Chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on a MULTI-LINK RX VISION or MULTI-LINK MINI VISION RX delivery system, respectively. Similarly, the XIENCE V OTW EECSS consists of the coated MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on a MULTI-LINK OTW VISION or MULTI-LINK MINI VISION OTW delivery system, respectively.

### 5.1 Stent

The XIENCE V Everolimus Eluting Coronary Stent (EECS) is a balloon expandable stent fabricated from a single piece of medical grade L-605 Cobalt Chromium (CoCr) alloy. This alloy can be formed into thinner stent struts than traditional stainless steel stents, and provides a more flexible, low delivery system profile while maintaining adequate radiopacity and strength.

**Design**

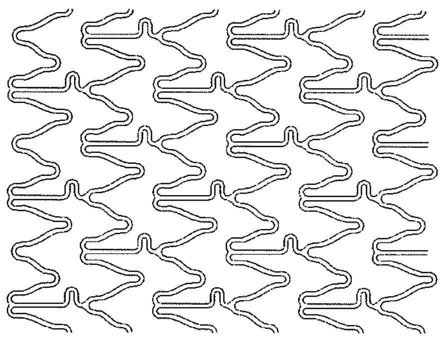
There are two stent designs for the XIENCE V EECS: small and medium. The small XIENCE V stent design (2.5, 2.75, and 3.0 mm diameters) is identical to the MULTI-LINK MINI VISION stent for the 2.5 diameter, and the MULTI-LINK VISION stent for the 2.75 mm and 3.0 mm diameter. The medium XIENCE V stent design is identical to the medium MULTI-LINK VISION stent for the 3.5 mm and 4.0 mm diameters. All stent diameters will be available in 8-28 mm lengths as shown in Table 5-1.

**Table 5-1 The XIENCE V Stent Sizes**

| Stent Design | Predicate Platform | Stent Diameter (mm) | Stent Lengths (mm) |
|---|---|---|---|
| Small | MINI VISION | 2.5 | 8, 12, 15, 18, 23, 28 |
| | VISION | 2.75 | 8, 12, 15, 18, 23, 28 |
| | VISION | 3.0 | 8, 12, 15, 18, 23, 28 |
| Medium | VISION | 3.5 | 8, 12, 15, 18, 23, 28 |
| | VISION | 4.0 | 8, 12, 15, 18, 23, 28 |

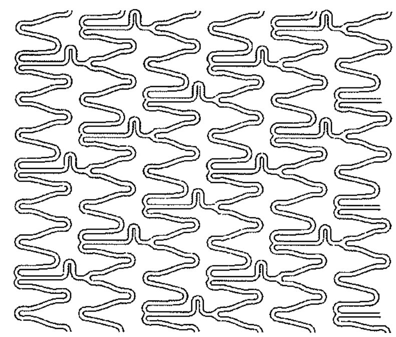
Figure 5-1 includes the stent expansion diameters, stent free area and several stent design features for both the small and medium XIENCE V stents. Figure 5-2 shows digital photographs of the small XIENCE V stent in its crimped and expanded state. Similarly, Figure 5-3 shows photographs of the medium XIENCE V stent in its crimped and expanded state.

**Small XIENCE V Stent**



| | |
|---|---|
| Expansion | Balloon expandable |
| Material | L-605 Cobalt-Chromium (CoCr) alloy |
| Expansion Diameters (mm) | 2.5, 2.75, and 3.0 (post-dilated to 3.5) |
| Lengths (mm) | 8, 12, 15, 18, 23, and 28 |
| Number of Crests per Ring | 6 |
| Number of Links per Ring | 3 |
| Strut Thickness (inch) | 0.0032 |

**Medium XIENCE V Stent**



| | |
|---|---|
| Expansion | Balloon expandable |
| Material | L-605 Cobalt-Chromium (CoCr) alloy |
| Expansion Diameters (mm) | 3.5 and 4.0 (post-dilated to 4.5) |
| Lengths (mm) | 8, 12, 15, 18, 23, and 28 |
| Number of Crests per Ring | 9 |
| Number of Links per Ring | 3 |
| Strut Thickness (inch) | 0.0032 |

**Figure 5-1 Description of the XIENCE V EECSS Stent Designs: The length, strut thickness, and number of links per ring are identical across designs while the expansion diameter and number of crests per ring varies.**

A.

B.

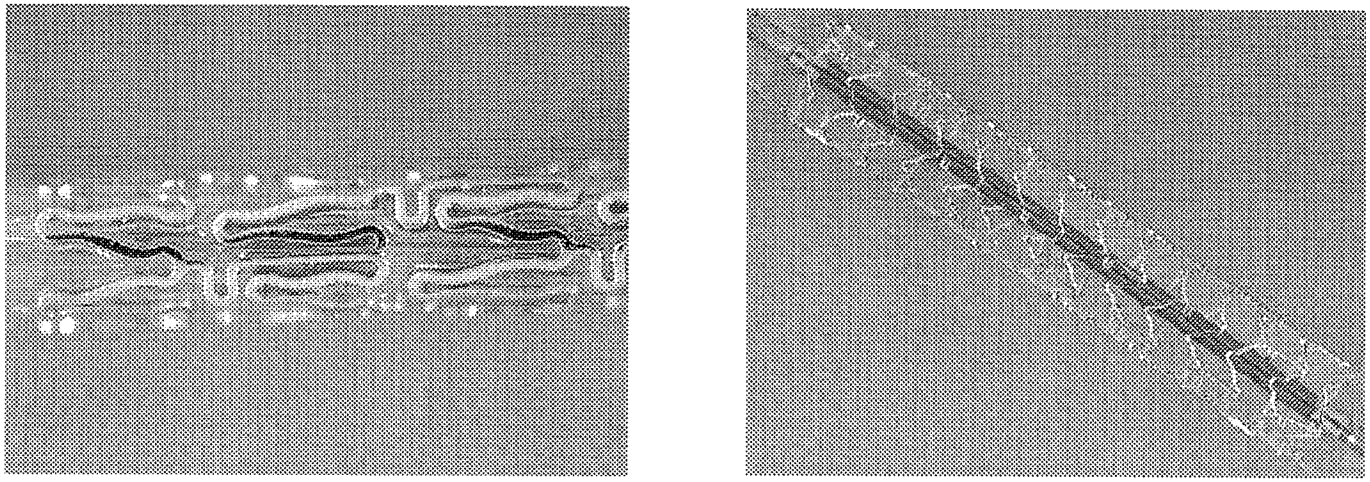


**Figure 5-2 Small XIENCE V Stent - Digital photographs showing the small XIENCE V stent in A) crimped and B) expanded forms**

A. B.

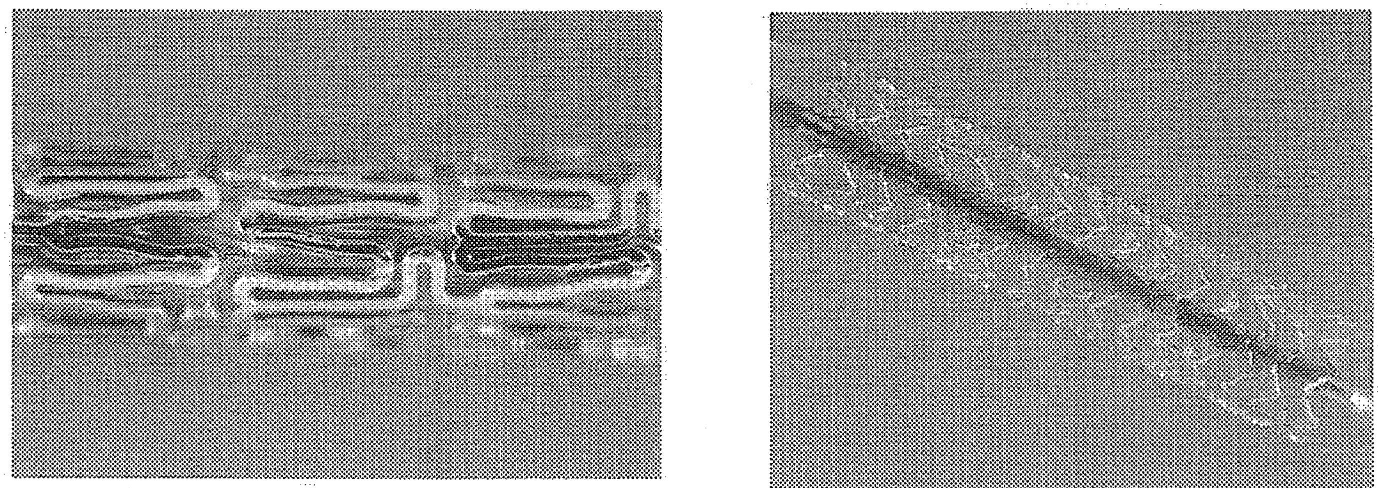


Figure 5-3 Medium XIENCE V Stent Design - Digital photographs showing the medium XIENCE V stent in A) crimped and B) expanded forms.

**Material**
The XIENCE V EECS is comprised of medical grade L-605 cobalt chromium (CoCr) alloy tubing conforming to ASTM Standard F90. A majority of the ASTM standards and test methods for L-605 CoCr alloy tubing generally refer to bar, wire, sheet, and strip testing. Abbott Vascular has adopted the relevant sections of these standards to ensure compliance with ASTM Standard F90.

### 5.2 Delivery System Platforms

The XIENCE V EECSS delivery system will be available in two platforms: the XIENCE V RX EECSS (Rapid Exchange (RX)) and the XIENCE V OTW EECSS (Over-the-Wire (OTW)). The balloon portions of these delivery systems are identical, the distal portions of these systems are identical in design and materials, and the proximal ends are specifically designed to accommodate either the RX or OTW platform. Figure 5-4 is a diagram of XIENCE V RX and OTW EECSS components.

A.

B.

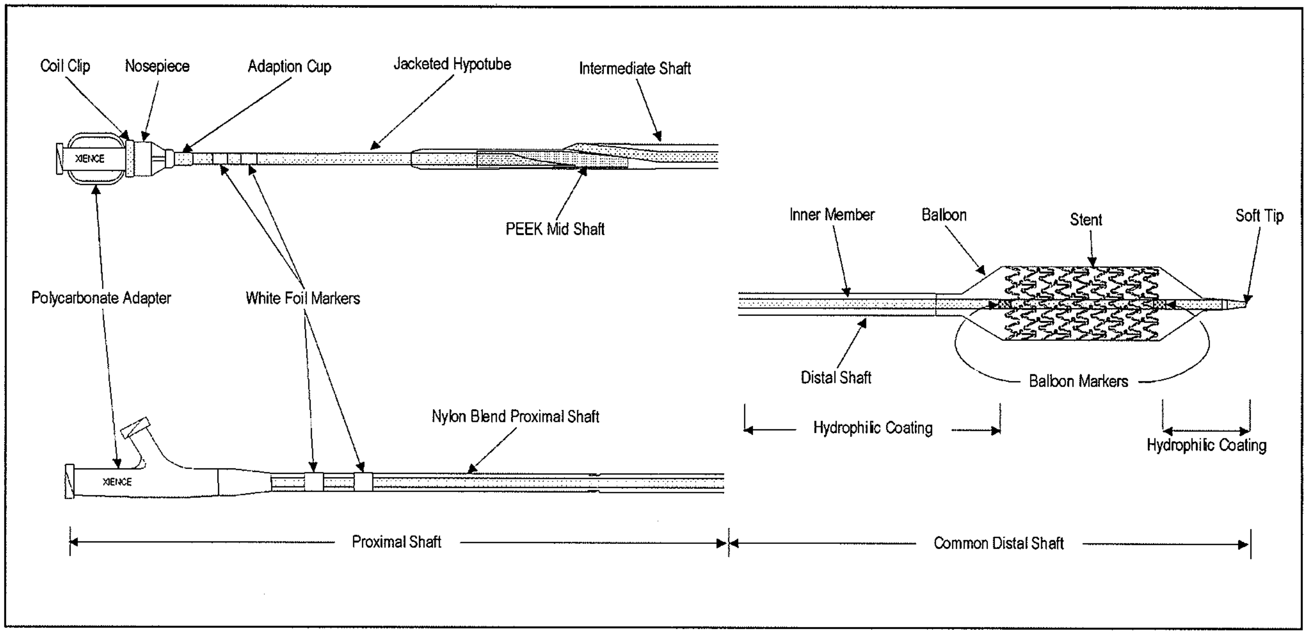



**Figure 5-4** **Similarities and Differences in Design between the XIENCE V RX and XIENCE V OTW EECSS. A diagram detailing A) XIENCE V RX and B) XIENCE V OTW Everolimus Eluting Coronary Stent System (EECSS). The proximal shaft comprises the unique features of these systems while the distal shaft is identical.**

### 5.2.1 The Rapid Exchange (RX) Delivery System

The XIENCE V RX EECSS is similar in design and performance specifications to the MULTI-LINK RX VISION CSS and the MULTI-LINK MINI VISION RX CSS.

**Design**

Like other Abbott Vascular RX coronary stent systems and coronary dilatation catheters, the XIENCE V RX EECSS combines a single lumen proximal shaft with a dual lumen mid-shaft and a co-axial lumen distal shaft to create the rapid exchange capability. The single lumen proximal shaft connects the intermediate/distal shaft with the inflation port of the catheter. The guide wire exit notch is located at the proximal end of the junction between the intermediate shaft and the mid-shaft support. The overall length of the catheter is 143 cm. Figure 5-5 illustrates the components and dimensions.

A single arm adapter is attached to the proximal end of the catheter and accesses the inflation/deflation lumen. The proximal shaft is thermally bonded to an adaptation cup that is mechanically sealed to the single arm adapter with a nosepiece, which is threaded to then bonded on the single arm adapter.

There are two non-radiopaque markers on the proximal shaft of the XIENCE V RX EECSS. The two markers, located 95 cm and 105 cm proximal to the distal tip, indicate when the distal tip of the catheter exits the tip of a brachial or femoral guiding catheter, respectively.

A 0.014-inch or smaller diameter guide wire can be used in the guide wire lumen. The guide wire exits the guide wire lumen at the guide wire exit notch, which is formed at the junction of the mid-shaft and the intermediate shafts. Proximal to this point, the guide wire runs externally alongside the proximal shaft of the catheter.

Two radiopaque balloon markers located on the distal segment of the inner member are positioned to mark the working length of the balloon. The stent is mounted such that the markers reflect the expanded stent length. The radiopaque markers fluoroscopically aid in positioning the stent and the delivery system for post-deployment dilation during the procedure.

Table 5-2 includes the product labeling specifications for the XIENCE V RX EECSS. A detailed protocol for XIENCE V RX EECSS preparation will be included in the "Instructions for Use" (IFU) provided with the product.

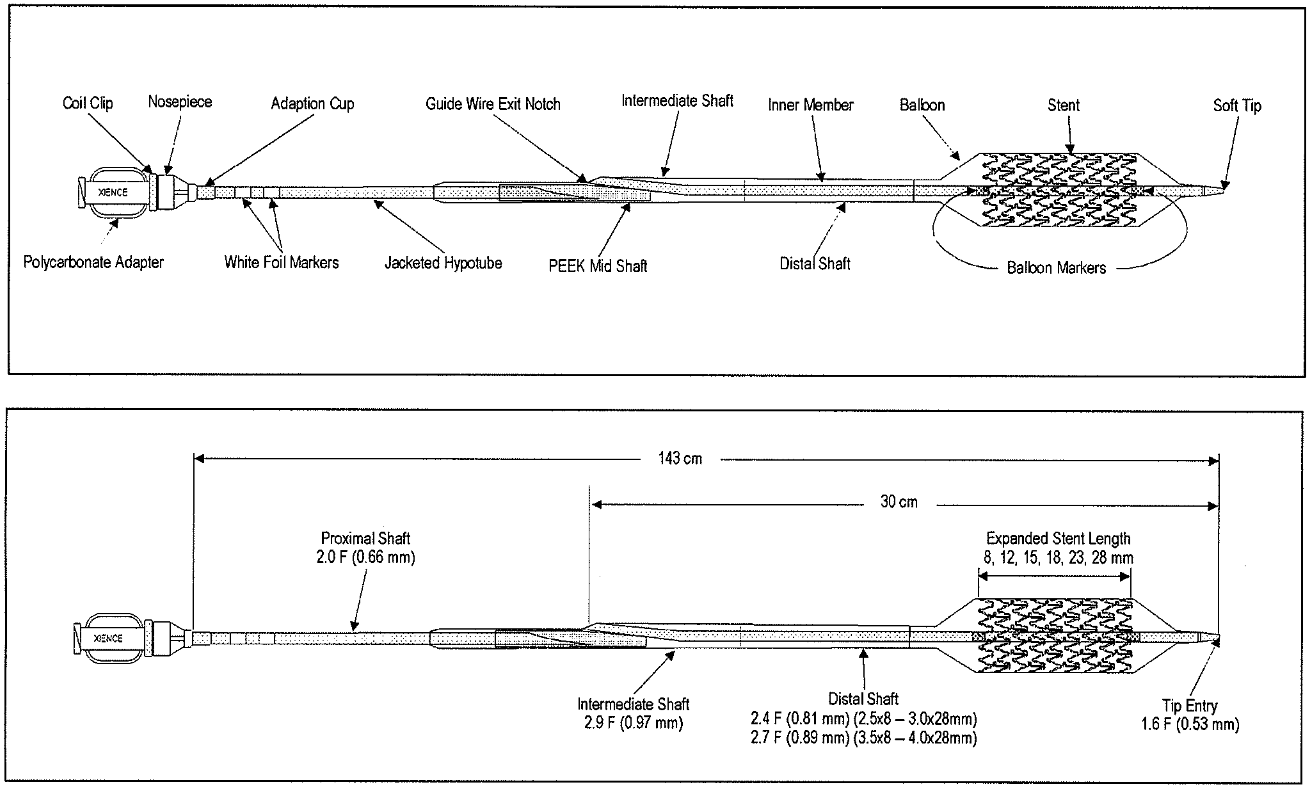



**Figure 5-5 The XIENCE V RX EECSS Components and Dimensions (Not to Scale). All dimensions are nominal.**

**Table 5-2 Device Specifications for the XIENCE V RX EECSS**

| Model Number | Stent Diameter (mm) | Stent Length (mm) | Crimped Stent Profile (in) | Rated Burst Pressure (atm) | System Working Length (cm) |
|---|---|---|---|---|---|
| 1009539-08 | 2.5 | 8 | 0.043” | 16 | 143 |
| 1009539-12 | 2.5 | 12 | 0.043” | 16 | 143 |
| 1009539-15 | 2.5 | 15 | 0.043” | 16 | 143 |
| 1009539-18 | 2.5 | 18 | 0.043” | 16 | 143 |
| 1009539-23 | 2.5 | 23 | 0.043” | 16 | 143 |
| 1009539-28 | 2.5 | 28 | 0.043” | 16 | 143 |
| 1009540-08 | 2.75 | 8 | 0.043” | 16 | 143 |
| 1009540-12 | 2.75 | 12 | 0.043” | 16 | 143 |
| 1009540-15 | 2.75 | 15 | 0.043” | 16 | 143 |
| 1009540-18 | 2.75 | 18 | 0.043” | 16 | 143 |
| 1009540-23 | 2.75 | 23 | 0.043” | 16 | 143 |
| 1009540-28 | 2.75 | 28 | 0.043” | 16 | 143 |
| 1009541-08 | 3.0 | 8 | 0.043” | 16 | 143 |
| 1009541-12 | 3.0 | 12 | 0.043” | 16 | 143 |
| 1009541-15 | 3.0 | 15 | 0.043” | 16 | 143 |
| 1009541-18 | 3.0 | 18 | 0.043” | 16 | 143 |
| 1009541-23 | 3.0 | 23 | 0.043” | 16 | 143 |
| 1009541-28 | 3.0 | 28 | 0.043” | 16 | 143 |
| 1009542-08 | 3.5 | 8 | 0.048” | 16 | 143 |
| 1009542-12 | 3.5 | 12 | 0.048” | 16 | 143 |
| 1009542-15 | 3.5 | 15 | 0.048” | 16 | 143 |
| 1009542-18 | 3.5 | 18 | 0.048” | 16 | 143 |
| 1009542-23 | 3.5 | 23 | 0.048” | 16 | 143 |
| 1009542-28 | 3.5 | 28 | 0.048” | 16 | 143 |
| 1009543-08 | 4.0 | 8 | 0.050” | 16 | 143 |
| 1009543-12 | 4.0 | 12 | 0.050” | 16 | 143 |
| 1009543-15 | 4.0 | 15 | 0.050” | 16 | 143 |
| 1009543-18 | 4.0 | 18 | 0.050” | 16 | 143 |
| 1009543-23 | 4.0 | 23 | 0.050” | 16 | 143 |
| 1009543-28 | 4.0 | 28 | 0.050” | 16 | 143 |

Note: All dimensions are nominal.

### 5.2.2 The Over-the-Wire (OTW) Delivery System

The XIENCE V OTW EECSS is similar in design and performance specifications to the MULTI-LINK OTW VISION CSS and the MULTI-LINK MINI VISION OTW CSS.

**Design**

Like other Abbott Vascular OTW coronary stent systems and coronary dilatation catheters, the XIENCE V OTW EECSS is comprised of a coaxially designed shaft with a balloon near the distal tip. The coaxial shaft consists of a tubular inner and outer member. The annular space between the inner and outer members provides a lumen for inflating and deflating the balloon; it is accessed through the side arm of the proximal adapter. The inner member of the system permits the use of a guide wire. The overall length of the catheter is 143 cm (Figure 5-6).

A sidearm adapter is attached to the proximal end of the catheter to access the inflation/deflation lumen and guide wire lumen. A strain relief provides a transition from the adapter to the shaft.

There are two non-radiopaque markers on the proximal shaft of the XIENCE V OTW EECSS located 95 cm and 105 cm proximal to the distal tip. These markers indicate when the distal tip of the catheter exits the tip of a brachial or femoral guiding catheter, respectively.

A 0.014-inch or smaller diameter guide wire can be used in the guide wire lumen. The guide wire lumen extends from the distal tip to the center port of the sidearm adapter.

Two radiopaque balloon markers are positioned on the distal segment of the inner member to mark the working length of the balloon. The stent is mounted in a manner permitting the markers to reflect the expanded stent length during fluoroscopic positioning of the stent as well as in situating the delivery system for post-deployment dilatation.

Table 5-3 includes the product labeling specifications for the XIENCE V OTW EECSS. A detailed protocol for XIENCE V OTW EECSS preparation will be included in the "Instructions for Use" (IFU) which will be provided with the product.

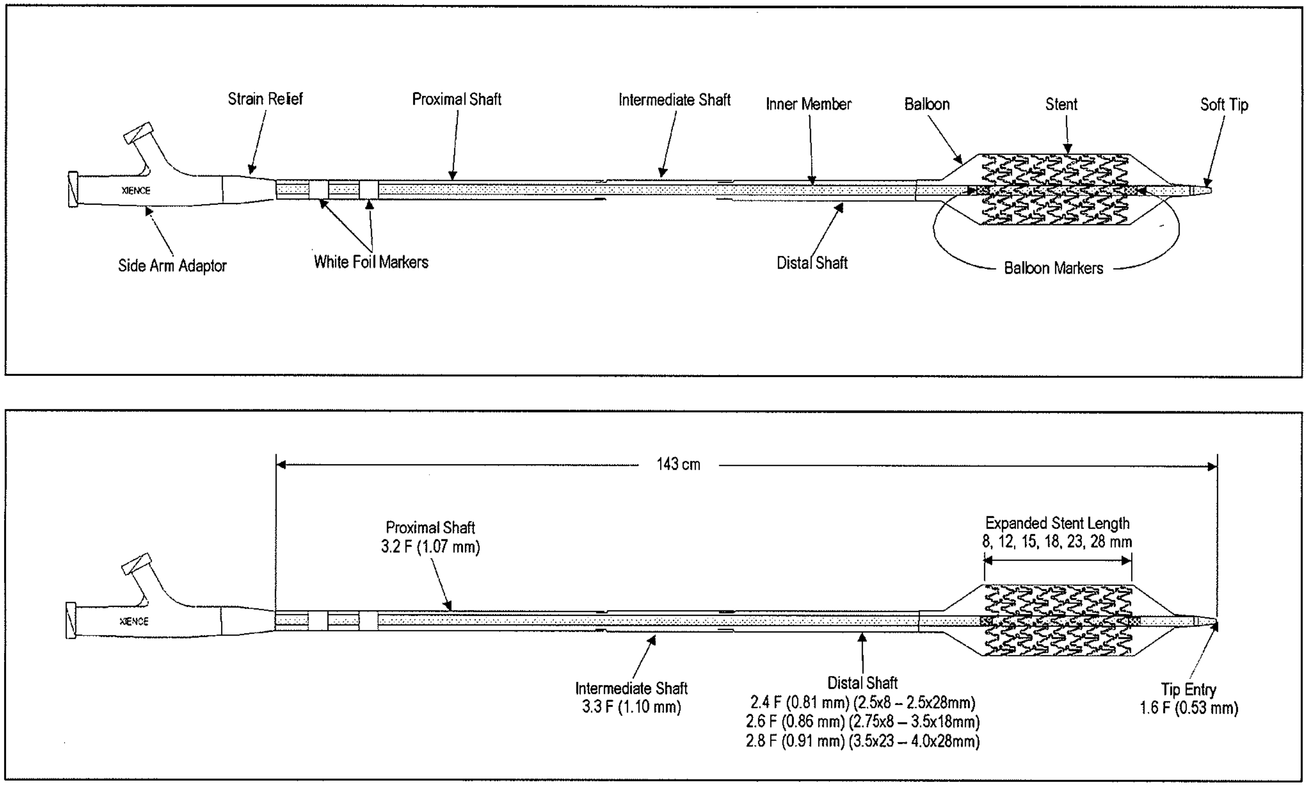



**Figure 5-6 The XIENCE V OTW EECSS Components and Dimensions (Not to Scale). All dimensions are nominal.**

**Table 5-3 Device Specifications for the XIENCE V OTW EECSS**

| Model Number | Stent Diameter (mm) | Stent Length (mm) | Crimped Stent Profile (in) | Rated Burst Pressure (atm) | System Working Length (cm) |
|---|---|---|---|---|---|
| 1009545-08 | 2.5 | 8 | 0.043" | 16 | 143 |
| 1009545-12 | 2.5 | 12 | 0.043" | 16 | 143 |
| 1009545-15 | 2.5 | 15 | 0.043" | 16 | 143 |
| 1009545-18 | 2.5 | 18 | 0.043" | 16 | 143 |
| 1009545-23 | 2.5 | 23 | 0.043" | 16 | 143 |
| 1009545-28 | 2.5 | 28 | 0.043" | 16 | 143 |
| 1009546-08 | 2.75 | 8 | 0.043" | 16 | 143 |
| 1009546-12 | 2.75 | 12 | 0.043" | 16 | 143 |
| 1009546-15 | 2.75 | 15 | 0.043" | 16 | 143 |
| 1009546-18 | 2.75 | 18 | 0.043" | 16 | 143 |
| 1009546-23 | 2.75 | 23 | 0.043" | 16 | 143 |
| 1009546-28 | 2.75 | 28 | 0.043" | 16 | 143 |
| 1009547-08 | 3.0 | 8 | 0.043" | 16 | 143 |
| 1009547-12 | 3.0 | 12 | 0.043" | 16 | 143 |
| 1009547-15 | 3.0 | 15 | 0.043" | 16 | 143 |
| 1009547-18 | 3.0 | 18 | 0.043" | 16 | 143 |
| 1009547-23 | 3.0 | 23 | 0.043" | 16 | 143 |
| 1009547-28 | 3.0 | 28 | 0.043" | 16 | 143 |
| 1009548-08 | 3.5 | 8 | 0.048" | 16 | 143 |
| 1009548-12 | 3.5 | 12 | 0.048" | 16 | 143 |
| 1009548-15 | 3.5 | 15 | 0.048" | 16 | 143 |
| 1009548-18 | 3.5 | 18 | 0.048" | 16 | 143 |
| 1009548-23 | 3.5 | 23 | 0.048" | 16 | 143 |
| 1009548-28 | 3.5 | 28 | 0.048" | 16 | 143 |
| 1009549-08 | 4.0 | 8 | 0.050" | 16 | 143 |
| 1009549-12 | 4.0 | 12 | 0.050" | 16 | 143 |
| 1009549-15 | 4.0 | 15 | 0.050" | 16 | 143 |
| 1009549-18 | 4.0 | 18 | 0.050" | 16 | 143 |
| 1009549-23 | 4.0 | 23 | 0.050" | 16 | 143 |
| 1009549-28 | 4.0 | 28 | 0.050" | 16 | 143 |

Note: All dimensions are nominal.

**Materials**
The XIENCE V RX EECSS and the MULTI-LINK RX VISION and MINI VISION RX delivery systems are identical in materials except for the addition of the primer and drug matrix polymers and the anti-proliferative drug for the XIENCE V platform. Similarly, the XIENCE V OTW EECSS and the MULTI-LINK OTW VISION and MINI VISION OTW delivery systems are identical in materials except for the addition of the primer and drug matrix polymers and the anti-proliferative drug for the XIENCE V platform. There is a difference in stent sheath material between the XIENCE V and VISION/MINI VISION systems. This sheath material has been evaluated within biocompatibility and engineering studies with no adverse effect.

## 5.3 Stent Coating

The XIENCE V EECSS has a coating consisting of two layers: a primer layer and a drug matrix layer. The primer layer is composed of an acrylic polymer and has been approved for other blood contacting applications. The drug matrix layer consists of a durable copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP) blended with the anti-proliferative drug everolimus (Certican®, Novartis Pharmaceuticals Corporation) in an 83%/17% (w:w) proportion respectively and applied to the entire surface (ie, luminal and abluminal) of the primer coated stent. PVDF-HFP is also a component of an approved blood contacting product. PVDF-HFP is blended with everolimus, which is under review in the US for the prevention of organ transplant rejection. Certican (everolimus) has obtained market authorization in over 65 countries. No topcoat layer is used. Figure 5-7 contains scanned electron microscopy (SEM) images of the coated XIENCE V stent in both crimped and expanded states.

**Crimped** **Expanded**

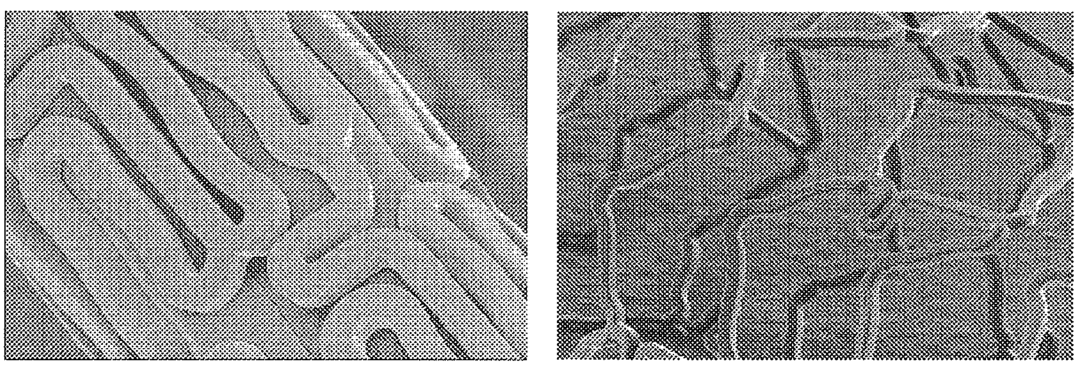


**Figure 5-7 Scanned Electron Microscopy (SEM) Images. Images of the coated XIENCE V stent serpentine rings connected by links in both the crimped (60x magnification) and expanded (45x magnification) state.**

### 5.3.1 The Primer Coating

The primer coating is used to improve the adhesion between the L-605 CoCr alloy MULTI-LINK VISION stent and the PVDF-HFP drug matrix. The primer coating which renders it resistant to hydrolytic and enzymatic degradation *in vivo*[1].

## 5.3.2 The Drug Matrix

PVDF-HFP is a random copolymer made from vinylidene fluoride (VDF) and hexafluoropropylene (HFP) monomers. The copolymer is semi-crystalline with glass transition and melting temperatures of respectively. The VDF unit in the polymer contains one secondary and one quaternary carbon, while the HFP unit in the polymer is perfluorinated. The high dissociation energy of the C-F bond coupled with the absence of other atoms in the backbone (ie, oxygen, nitrogen, sulfur) renders PVDF-HFP resistant to process-induced degradation, oxidative degradation *in vivo*, and free radical induced degradation *in vivo*. Also, PVDF-HFP contains no reactive functional groups and is stable at physiological conditions (Figure 5-8). Additionally, the elongation strain for the fluoropolymer is approximately while the L-605 Cobalt Chromium hypotube can tolerate an elongation strain of 30% its original length. Therefore, coating-related tension failure is not expected to occur. Due to the dissimilarity of the balloon material (Pebax) and PVDF-HFP polymer, the stent coating does not adhere to the balloon material.

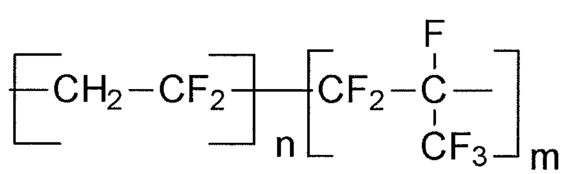


**Figure 5-8 Formula for Vinylidene Fluoride and Hexafluoropropylene Copolymer (PVDF-HFP)**

PVDF-HFP was chosen as the drug matrix polymer because it met the design objectives for the XIENCE V stent. This material has a history of use in approved coronary applications and proven vascular compatibility, showed excellent mechanical coating integrity, was stable *in vitro* and *in vivo*, showed compatible solubility, coatability and sterilizability, was available in a high purity grade, and demonstrated drug permeability.

---

1 Mark, James E, ed. Physical properties of polymers handbook. Woodbury, N.Y.: American Institute of Physics, 1996, p605-607

2 Baker, R, Controlled Release of Biologically Active Materials, Wiley-Interscience, 1987, Chapter 3

PVDF-HFP worked well in a simple matrix design, which after evaluating a number of other release systems, was chosen for the XIENCE V system due to the good coating quality and integrity, versatility and reproducibility of the release profile, and ease of manufacturing.

The simple matrix systems consisted of physical blends of drug and PVDF-HFP. Matrix designs are the most manufacturable. A classical matrix system, with solid drug dispersed in a matrix of polymer saturated with drug will release the drug according to a profile that is linear with the square root of time for a significant fraction of its release[3]. Developmental studies showed that by varying the drug to polymer (D:P) ratio and the thickness of the coating, a wide range of release rates could be achieved, and that these release rates were well controlled and reproducible.

The release of the drug from the XIENCE V stent as measured in animal studies is shown in Figure 5-9. This figure shows how the controlled release of everolimus from the XIENCE V stent correlates to the *in vivo* restenosis cascade[4].

---

[3] Baker, R,Controlled Release of Biologically Active Materials, Wiley-Interscience, 1987, Chapter

[4] Forrester JS et al. A Paradigm for Restenosis based on Cell Biology: Clues for the Development of New Preventative Therapies. JACC 1991, Vol 17, No 3, 758-69

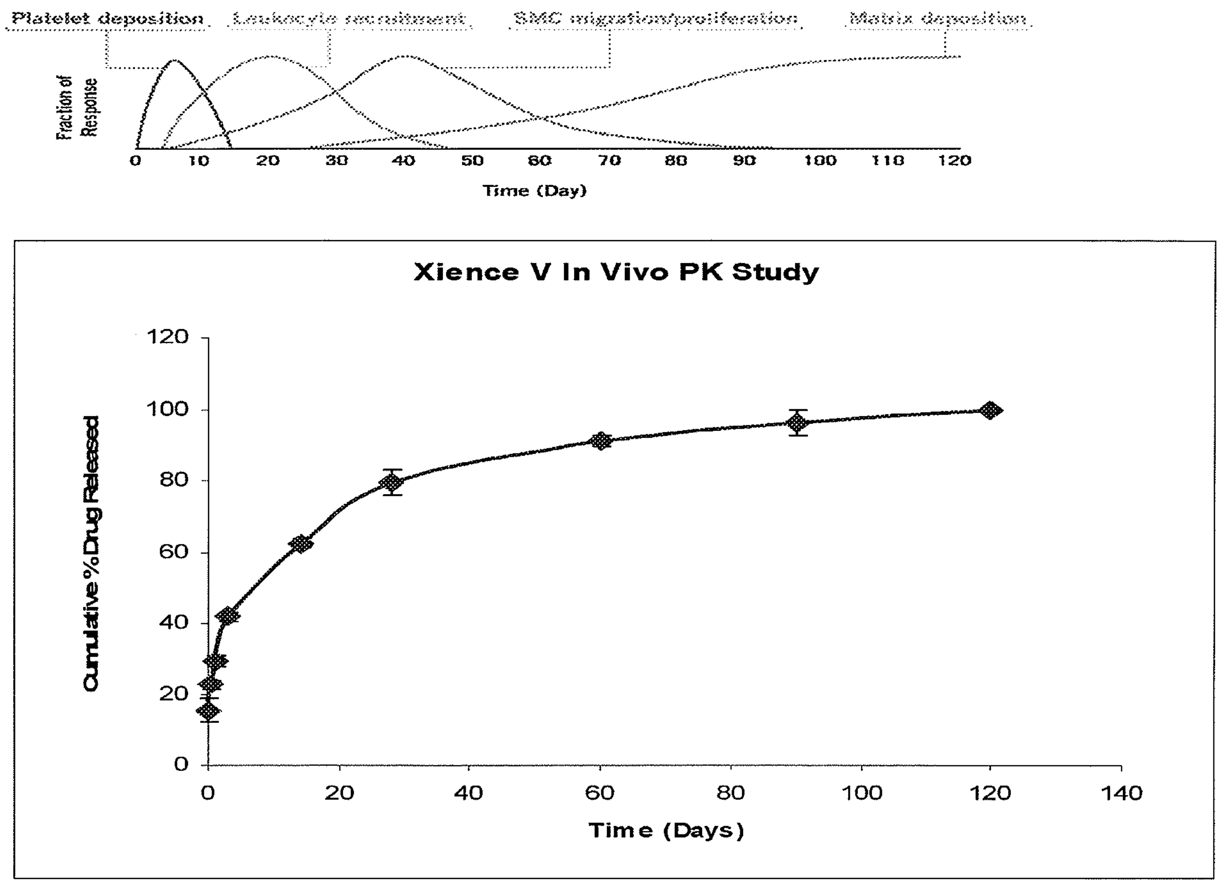



**Figure 5-9 Release of Everolimus from the XIENCE V Stent compared to Restenosis Cascade as shown in Animal Pharmacokinetic Studies**

### 5.3.3 The Anti-Proliferative Drug: Everolimus

The active pharmaceutical ingredient in the XIENCE V EECS system is everolimus [40-O-(2-hydroxyethyl)-rapamycin], provided to Abbott Vascular by Novartis Pharmaceuticals Corporation. Everolimus is a novel semi-synthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: sirolimus) is a secondary macrolide metabolite produced by certain actinomycete strains. The structure of everolimus (Figure 5-10) consists of a 2-hydroxyethyl group in position 40 of sirolimus. Sirolimus (Rapamune®; Wyeth) has received global marketing approval for the prophylaxis of renal transplant rejection. In numerous clinical trials, sirolimus used as an adjunctive coating on coronary stents, has been shown to prevent restenosis. A sirolimus-eluting stent has obtained marketing approval in the European Union, Canada, Japan, and the US. Everolimus is a drug that has been evaluated in clinical trials in the US and outside the US for use in conjunction with other medications to prevent heart and renal transplant rejection. Everolimus (Certican) has obtained market approval in over 65 countries.

Additionally, everolimus (Certican) is under review for market approval in the United States and has received two approvable letters from FDA. Novartis continues to work with the FDA towards a final NDA decision using additional clinical data from prospective transplant trials that evaluate a regimen of everolimus with therapeutic drug monitoring and reduced dose Neoral® (cyclosporine, USP) MODIFIED to support the NDA review.

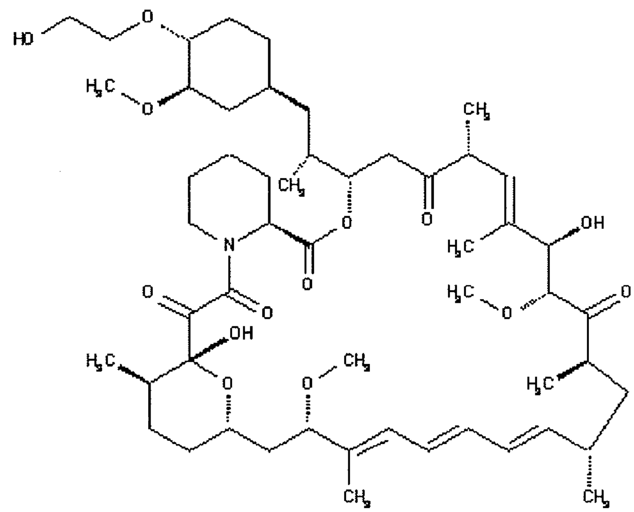


**Figure 5-10 Structure of Everolimus**

### 5.3.3.1 Everolimus Mechanism of Action

In comparison with rapamycin, an immunosuppressant of the same class of macrolide compounds, everolimus showed similar systemic exposure and toxicity profiles in pre-clinical studies. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1, two key players in the initiation of protein synthesis, is inhibited. Although not formally proven, it is thought that the everolimus-FKBP-12 complex may bind and interfere with FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin) - a protein that governs cell metabolism, growth and proliferation, and regulates phosphorylation of both p70 S6 kinase and 4E-BP1. This is supported by modeling results using published X-ray structure information which suggest that there is no impediment to the ternary FKBP-12/everolimus/FRAP complex formation.

Everolimus possesses anti-fungal, immunosuppressive and anti-proliferating properties. Under the trade name Certican, everolimus has been studied in preclinical and clinical studies as an anti-rejection therapy used in combination with Neoral (cyclosporine, CsA). Everolimus is an

effective immunosuppressive agent that can act synergistically with CsA for the prophylaxis of acute rejection while concomitantly preventing smooth muscle cell proliferation at the level of the graft vessel.

**5.3.3.2 Summary of Novartis' Preclinical Data on Certican**

**Overview of Preclinical Studies**

The potential of everolimus as an immunosuppressant in the indication of solid organ transplantation was demonstrated in rodent and non-human primate models of solid organ allotransplantation using an experimental microemulsion formulation of everolimus for oral application of the compound. Everolimus was well tolerated after single oral administration in acute toxicity studies, and therefore, it has a low potential to affect vital functions following accidental or deliberate overdosing.

In repeated-dose toxicity studies, effects secondary to immunosuppression were evident at higher dosages in all species, and indicate a potential of everolimus to exacerbate infectious background diseases. Major target organs in all animal species were reproductive organs, and males were generally more affected than females. Lesions were most probably related to an endocrine imbalance. This was evidenced in rats by a decrease in plasma testosterone levels as a consequence of an inhibition of key regulators of steroid hormone synthesis. Lungs (increased alveolar macrophages) were identified as rodent-specific target organs, and eyes (lenticular anterior suture line opacities) as rat-specific target organs.

Everolimus was devoid of mutagenic or clastogenic activity, and did not show an oncogenic potential. In reproduction studies, orally administered everolimus was toxic to the conceptus in rats and rabbits. It is therefore recommended that women of childbearing potential should use effective contraceptive measures during the entire treatment period. If women are in early pregnancy when treatment starts, they should be informed about the potential risk to the fetus. In view of the absence of genotoxic effects and the results from male fertility studies, male patients who receive treatment with everolimus should not be prohibited from attempting to father children.

**Carcinogenicity Studies**

In the mouse and rat 104-week carcinogenicity studies, there was no indication of a tumorigenic potential up to the high dose of 0.9 mg/kg of everolimus, corresponding to an exposure ratio of 8.6 and 0.3, respectively, relative to the maximum recommended dose of 3 mg/day for man.

**Reproductive Toxicology Studies**

In the 13-week male fertility study in rats, no treatment-related effects were noted at the lowest dose of 0.1 mg/kg. At 0.5 mg/kg, a slight effect on testicular morphology was detected, but there was no difference from

controls in animals after 13 weeks of recovery. There were no adverse effects on reproductive parameters at this dose. At the highest dose of 5.0 mg/kg, males mated, but none of the females became pregnant. Males at 5.0 mg/kg showed marked histopathological changes in the testes (atrophy with germ cell depletion) and epididymides (oligospermia to aspermia). Sperm motility and testicular sperm head count were diminished. Plasma testosterone levels were significantly reduced. After a 13-week recovery period, reversibility of the histopathological changes was complete in only half of the animals, and pregnancy was confirmed in 13/18 inseminated females mated with the treated males. There was no evidence of adverse effects by treating males with everolimus on embryo-fetal parameters.

Female fertility was not affected, but everolimus crossed the placenta, and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity that was manifested as mortality and reduced fetal weight. Increased incidence of skeletal retardation, fetuses with 14 ribs and spontaneous malformations was reported. In rabbits, embryotoxicity was evidenced by an increase in late resorptions.

Effects of everolimus on the pre- and post-natal development of rats did not indicate a specific toxic potential.

**Mutagenicity Studies**

Everolimus was tested for genotoxic activity in a variety of *in vitro* and *in vivo* tests, covering all relevant endpoints. There was no evidence of a mutagenic or clastogenic activity. Everolimus exposure in the mouse at the doses used in the micronucleus assay was well in excess of that expected at therapeutic doses in humans.

**Special and Combination Toxicity Studies**

Everolimus did not show a potential to cause contact hypersensitivity on the skin of guinea pigs in the maximization test. Everolimus was not irritating to the skin of rabbits.

The administration of everolimus in combination with CsA to rats and monkeys resulted in changes related to the pharmacological activity of the compounds, and in findings reflecting toxicity, both notably exacerbated when compared to those observed with each of the compounds alone. There were no new target organs in the rat.

Monkeys treated with combinations of everolimus and CsA showed unexpected findings of hemorrhage and arteritis in several organs (gastrointestinal tract [GI] tract, heart, liver, kidneys, lymph nodes and pancreas). In view of the complexity of the possible involved mechanisms, the pathogenesis of arteritis remains uncertain, although the high degree of immunosuppression in connection with a disturbed integrity of the gut could suggest an infectious/inflammatory origin. The low-dose

combination of CsA/everolimus at 50/0.25 mg/kg resulted in a higher degree of immunosuppression than with the compounds alone, but was not associated with arteritis or poor health status as observed with the high-dose combinations.

The combination of everolimus and tacrolimus in rats induced an increased severity of adverse effects and of changes related to immunosuppression when compared with those of either compound alone. The increase in toxicity was particularly pronounced in the cardiovascular and reproductive systems. With the low-dose combination of everolimus and tacrolimus, both at 0.75 mg/kg, there was, however, only slight increases in severity compared with each compound alone. The combination had no relevant effect on the toxicokinetic profile of tacrolimus, whereas exposure with everolimus was markedly increased.

**Absorption and Bioavailability**
A significant proportion of the absorbed everolimus in the rat, especially at low oral doses, was affected by intestinal first-pass metabolism[5]. The absolute bioavailability of everolimus was 5% in the mouse, 14%-26% in the rat and 6% in the monkey. Studies in Caco-2 cells showed that everolimus was a substrate for the efflux transporter P-gp at low concentrations, but that this efflux was saturated at higher concentrations[6]. The absolute bioavailability of everolimus could not be assessed in man due to the difficulties in providing an appropriate formulation for intravenous administration, and since no non-toxic effect level was identified in the intravenous monkey studies.

**Distribution**
The *in vitro* distribution of everolimus between blood cells and plasma was concentration dependent over the range of 5 to 5000 ng/mL in the rat, monkey and human, and concentration independent in the mouse.

Everolimus was highly bound to plasma proteins of the mouse (99.9%), and moderately bound in the rat (92%), monkey (84%) and human (75%). The moderate affinity of everolimus for human plasma proteins indicates that a potential drug-drug interaction on the basis of drug protein binding is very unlikely. The extent of protein binding was similar between healthy humans and patients with moderate hepatic impairment.

---

[5] Crowe A, Bruelisauer A, Duerr L, et al (1999) Absorption and intestinal metabolism of SDZ-RAD and rapamycin in rats. Drug Metab Dispos; 27(5):627-632.
[6] Crowe A, Lemaire M (1998) *In vitro* and *in vivo* absorption of SDZ RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: Comparison with rapamycin. Pharm Res; 15:1666-1672.

**Metabolism**
The metabolism of everolimus was investigated in the mouse, rat and monkey after single oral and intravenous doses. In humans, the metabolism of everolimus was investigated in stable renal transplant patients on Neoral after a single oral dose of 3 mg [$^{14}$C]everolimus.

In all species, generally, the parent drug was the major circulating component in blood, averaging 31%-63% of the total $AUC_{(0-24\,h)}$ radioactivity in mice, rats and humans and 12% in the monkey. In human blood, 5 major metabolite peaks were present covering, together with unchanged drug, > 80% of the total $^{14}$C-AUC. These 5 main metabolites detected in human blood were also present in the blood of the mouse, rat and monkey.

**Excretion/Elimination**
Excretion of everolimus and its metabolites was predominantly via feces in all investigated species, including man, and was characterized by metabolic clearance. Virtually no parent drug was recovered in the urine and feces. The balance of excretion was almost complete within several days.

**Drug-Drug Interaction Potential**
The potential for metabolic drug-drug interactions was investigated *in vitro* in human liver microsomes, and in microsomes from recombinant CHO cells expressing individual cytochrome P450 isoenzymes. CYP3A4 was the major P450 enzyme involved in the microsomal biotransformation of everolimus (Km 2-3 µmol/L; $V_{max}$ 46-100 nmol/h/mg microsomal protein)[7].

Everolimus was a competitive inhibitor of the CYP3A substrate CsA ($K_i$ = 2.3 µmol/L), and was also a mixed inhibitor of the CYP2D6 substrate dextromethorphan ($K_i$ = 1.7 µmol/L). The maximum plasma concentration following a daily recommended highest oral dose of 1.5 mg bid of everolimus in human ($C_{max}$ss: 20.3 ± 8.0 ng/mL) was, however, more than 75-fold below these $K_i$-values. Therefore, everolimus is unlikely to significantly affect the metabolism of other compounds predominantly cleared by these enzymes.

**Prevention of Vascular Proliferation**
Everolimus inhibited *in vitro* fetal calf serum-stimulated bovine aortic smooth muscle cell (SMC) proliferation. Oral administration of everolimus (1.0 mg/kg/day, beginning 3 days before vessel injury) to pigs inhibited PTCA-induced intimal thickening by 54% and neointimal area by

---

[7] Kuhn B, Jacobsen W, Christians U, et al (2001) Metabolism of sirolimus and its derivative everolimus by cytochrome P450 3A4: Insights from docking, molecular dynamics and quantum chemical calculations. J Med Chem; 44:2027-2034.

34%. Additionally, everolimus was efficacious in a rabbit stent model. Rabbits were treated with 2 different oral dosing regimens of everolimus in combination with arterial stenting. The high dose regimen consisted of 1.5 mg/kg/day beginning 3 days prior to stenting and continuing for 14 days following stenting, after which the dose was reduced to 1.0 mg/kg/day for the remainder of the study. The low dose regimen consisted of 1.5 mg/kg/day the day before surgery, which was then reduced to 0.75 mg/kg/day for the remainder of the study. At 28 days post stenting both groups showed 84% endothelialization of the stent. Both treatment regimens significantly reduced neointimal thickness (by 49% for the high dose and 40% for the low dose) and neointimal area (by 32% for the high dose and 24% for the low dose).

These data supported the further investigation of everolimus as a potential therapeutic agent for the reduction of restenosis following PTCA and stenting. In order to avoid the potential side effects and large doses associated with oral administration of everolimus, Abbott Vascular has studied the safety and potential utility of everolimus eluting stents for the prevention of restenosis.

### 5.3.3.3 Summary of Novartis' Clinical Data on Certican

The purpose of the following discussion is to summarize the safety and efficacy of systemically administered everolimus. Everolimus has been studied extensively in renal and heart transplantation with additional date in lung and liver transplant patients. Therapeutic doses between 1.5 and 3.0 mg/day have been thoroughly evaluated. The use of everolimus in heart transplant studies showed significantly less thickening of the intima in the coronary arteries of transplanted patients in comparison with the control group. These findings support the safety and efficacy of everolimus at doses that exceed the levels eluted from the XIENCE stent. The following data are from Novartis Investigator's Brochure, Edition 9, dated August 27, 2007.

Everolimus, at therapeutic blood levels greater than 3.0 ng/ml, has been shown to be an effective immunosuppressant that has been developed for use in combination with Neoral® (cyclosporine, USP) MODIFIED for the prophylaxis of acute rejection and the prevention of chronic rejection in patients receiving organ transplants. The following is a summary of clinical trials, demonstrating the safety profile of systemic therapeutic levels of everolimus greater than 3.0 ng/ml. Accordingly, the blood levels of everolimus achieved with oral doses used in clinical trials of organ transplant rejection are approximately ten-fold higher than the total *in vivo* systemic exposure with the implantation of XIENCE.

In humans, everolimus dosed twice daily (bid) with CsA yields steady-state drug exposure by day 4 after initiation of therapy in renal and heart transplant recipients. Thereafter, blood levels of drug remain relatively

constant over time through the first post-transplant year. There are no clinically relevant departures from dose proportionality in exposure. Freedom from acute rejection in both renal and heart transplantation is significantly related to everolimus trough concentrations with a lower therapeutic concentration threshold of 3 ng/mL. There is only a small additional increase in freedom from rejection at everolimus trough levels above 8 ng/mL. Although the incidence of decreased thrombocyte counts (< 75 to 100 x $10^9$/L) increases with increasing exposure, the overall incidence in clinical trials was low, and therefore, a precise upper concentration for the therapeutic range could not be identified based on safety concerns. Clinical experience with trough concentrations above 12 ng/mL or doses above 1.5 mg bid is limited. The therapeutic concentration range is recommended as 3 to 8 ng/mL in both kidney and heart transplantation.

**Use of Everolimus in Renal Transplantation**

***Efficacy Summary***

In *de novo* renal transplant patients, both doses of everolimus combined with full-dose Neoral had similar efficacy as compared with mycophenolate mofetil (MMF) for efficacy failure (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) at 6 and 12 months, and were comparable at 36 months. The therapeutic drug monitoring analyses strongly suggest that graft survival would be improved with the use of everolimus concentration monitoring. Patient survival was excellent in all groups.

In studies B251 and B201 in *de novo* renal transplant patients, both doses of everolimus (1.5 and 3 mg/day) administered in combination with Neoral and corticosteroids was equivalent to MMF with respect to efficacy failure at 6 months post-transplantation (ie, biopsy-proven acute rejection, graft loss, death, or loss to follow-up). Equivalence for efficacy failure was maintained at 12 months. For the co-primary endpoint of graft loss, death, or loss to follow-up at 12 months post-transplantation, in study B251 (mostly US centers), everolimus 3 mg was equivalent to MMF, and both 95% and 97.5% confidence intervals (CIs) for everolimus 1.5 mg vs. MMF slightly exceeded the limit of equivalence. In study B201 (mostly European centers), everolimus 1.5 mg was equivalent to MMF, and both 95% and 97.5% CIs for everolimus 3 mg vs. MMF slightly exceeded the limit of equivalence. The incidence of late-occurring biopsy-proven acute rejections (ie, days 451 to 1170) was low in all groups. Between 1 and 1170 days, the incidence of deaths was similar in all groups for studies B251 and B201, respectively: everolimus 1.5 mg - 12 patients (6%) / 15 patients (8%), everolimus 3 mg - 13 patients (7%) / 18 patients (9%), and MMF – 10 patients (5%) / 16 patients (8%).

As the use of everolimus with full-dose Neoral is associated with renal dysfunction in some renal patients, it has been important to recognize that

the efficacy of everolimus is maintained in combination with reduced-dose Neoral. This was initially demonstrated in study B156, a prospective trial using the 3 mg/day dose of everolimus, in which rejection efficacy remained excellent despite reduction of Neoral exposure by about 35%. Amendments to the Phase 3 studies showed that late rejection was very rare when CsA trough levels were reduced to about 75 ng/mL at 18-31 months after transplantation. This study demonstrated excellent efficacy in both the Neoral full- and reduced-dose groups, thus demonstrating that efficacy is maintained when CsA exposure is reduced in combination with everolimus.

The most recent renal studies A2306 (without Simulect) and A2307 (with Simulect induction), which both used TDM prospectively, demonstrated better renal function, at 12 months, than that previously observed in the phase 3 studies, B251, B201 and B156. Everolimus 1.5 and 3 mg in combination with corticosteroids and a reduced Neoral dose regimen was effective in the prevention of graft rejection after renal transplantation at 12 months post-transplant. The incidence of efficacy failure and biopsy-proven acute rejection was low in both studies, and comparable to that observed in the pivotal studies, B251 and B201, and study B156. Long term outcomes at 36 months in the A2306 and A2307 extensions were similar to those at 12 months and no statistically significant differences between groups were observed in efficacy and safety parameters.

***Safety Summary***

In *de novo* renal transplant patients, both fixed doses of everolimus (1.5 mg and 3 mg) were generally well-tolerated, although there was a tendency towards a higher incidence of nonfatal SAEs and discontinuations of study medication due to AEs with everolimus compared with MMF. Thrombocytopenia was observed more frequently in both everolimus groups compared with the MMF group. Everolimus plus full-dose CsA was associated with dose related increases in mean serum creatinine and decreases in creatinine clearance compared with MMF. Mean testosterone was significantly lower in both everolimus groups compared with the MMF group; however, at 12 months, mean testosterone was within the normal range in all treatment groups. Elevations of serum lipids occurred more frequently in everolimus-treated patients than in the MMF group, with greater changes in the everolimus 3 mg group compared with the 1.5 mg group.

In renal study A2306, with a reduced-dose Neoral regimen and concentration controlled everolimus, mean and median serum creatinine was low, and stable from 2 or 3 months onwards to 12 months. The inclusion of only approximately 50% of the original randomized patients into the extension of this study limits meaningful conclusions made for this extension.

**Use of Everolimus in Heart Transplantation**

***Efficacy Summary***

In the heart transplant study B253, both doses of everolimus (1.5 and 3 mg/day) were superior to azathioprine (AZA) for efficacy failure (acute rejection ISHLT ≥ grade 3A, acute rejection associated with hemodynamic compromise, graft loss, death, or loss to follow-up) at 6, 12, 24, and 48 months. This finding was primarily due to a reduction in the incidence of acute rejection (ISHLT ≥ grade 3A) in the everolimus groups. As discussed above for renal transplantation, TDM is expected to enhance the efficacy and safety of everolimus in heart transplantation. There is a clear reduction in the incidence of acute rejection with average everolimus trough levels > 3 ng/mL. A small subset of patients was enrolled up to 72 months prior to study discontinuation. The number of patients was too small to reach any conclusion of their data.

The heart study also demonstrated a significant reduction in average maximum intimal thickness of the coronary arteries from baseline at 12 and 24 months for both doses of everolimus compared with the AZA group. Thus, both doses of everolimus were superior with respect to the incidence of allograft vasculopathy at 1 year post-transplantation, and the 1.5 mg group was also superior at 24 months.

Everolimus, at fixed doses of 1.5 and 3 mg/day, administered in combination with Neoral and corticosteroids to primary heart allograft recipients was superior to a standard treatment with 1-3 mg/kg/day of AZA with regard to the incidence of efficacy failure at 6, 12, 24, and 48 months and everolimus 3 mg/day was superior to 1.5 mg/day. In particular, significantly fewer acute rejection episodes were reported in both everolimus dose groups, and this effect was dose related. Twelve, 24-, and 48-month patient and graft survival was excellent in all groups, with no significant differences between everolimus and AZA. Specifically, in the long-term, open-label extension period (48 months) between Days 1 and 1,530, the incidence of deaths was similar in all treatment groups: everolimus 1.5 mg - 32- patients (15.3%), everolimus 3 mg - 34 patients (16.1%), and AZA - 30 patients (14%).

***Safety Summary***

In *de novo* heart transplant patients, the incidence of nonfatal SAEs and discontinuations of study medication due to AEs was significantly higher in the 3 mg fixed dose of everolimus compared with the 1.5 mg fixed dose of everolimus and azathrioprint. The overall infection rates were comparable between groups; however, there was a significantly higher incidence of viral infections (particularly CMV infections) in the AZA group than in the everolimus groups. Decreases in mean hemoglobin and platelet counts occurred more frequently in everolimus-treated patients than in the AZA group, and were associated with everolimus dose level. Conversely, leukopenia was more frequent in the AZA group. Mean LDLs

and HDLs were not significantly different between groups. Mean triglycerides were elevated in both everolimus groups compared with the AZA group. Everolimus was associated with dose related increases in mean serum creatinine and decreases in creatinine clearance that were significant compared with the AZA group, but these values were stable from 12 to 24 months. Mean testosterone was significantly lower in both everolimus groups compared with the AZA group.

**Use of Everolimus in Lung Transplantation**
***Efficacy Summary***
In maintenance lung transplant patients (study B159), everolimus showed unique efficacy not only to prevent acute rejection, but also slowed the progression in airway dysfunction. The onset of bronchiolitis obliterans syndrome (BOS) in this patient population portends limited long-term survival. Everolimus 3 mg/day was superior to AZA 1-3 mg/kg/day for the primary efficacy endpoint (incidence of $FEV_1$ decline > 15% of the baseline value from the study entry value, graft loss, death or loss to follow-up during the first 12 months after the initial dose of study medication). The incidence rates for this composite primary endpoint were 22% and 34% for everolimus 3 mg/day and AZA, respectively ($p = 0.0455$). The incidence rate for $FEV_1$ > 15% was 16% vs. 28% ($p=0.034$), and for treated acute rejection episodes was 8% vs. 32% ($p < 0.001$), showing a significant advantage of everolimus vs. AZA, while the incidence of deaths (3% vs. 9%, $p = 0.061$) and all other secondary efficacy endpoints demonstrated a trend in favor of everolimus. More AZA patients discontinued study medication due to unsatisfactory therapeutic effects, while more patients discontinued study medication in the everolimus group due to AEs.

The primary efficacy endpoint (ie, incidence of $FEV_1$ decline >15% of the baseline value from study entry value, graft loss, death or loss to follow-up during the first 12 months after the initial dose of study medication) was 22% and 34% for everolimus 3 mg/day and AZA, respectively, and the difference in favor of everolimus was significant ($p = 0.0455$).

Graft losses and deaths were numerically lower in the everolimus group. Everolimus was superior to AZA with regard to the incidence of $FEV_1$ decline >15% of the baseline value from study entry value ($p = 0.034$). Everolimus was also superior to AZA with regard to the incidence of BOS and decline in $FEV_1$ >15% ($p = 0.014$) and the incidence of treated acute rejection episodes ($p < 0.001$). In addition, all other efficacy variables showed a trend in favor of everolimus.

By 24 months, the incidence of acute rejection remained significantly lower in the everolimus patients as compared to AZA. However, the incidence of the primary composite endpoint did not differ between treatment groups (everolimus: 43.6%; AZA: 44.6%) and rates of graft loss

and death were similar. The incidences of $\Delta FEV_1 > 15\%$ (34.7% vs 41.1%) and all other secondary efficacy endpoints were numerically lower in the everolimus group. There was also a trend in favor of everolimus with regard to the mean decline in $FEV_1$ from study entry to 24 months.

***Safety Summary***

Everolimus use in lung transplantation (study B159) was associated with its anticipated side effect profile of CsA nephrotoxicity, lipid elevation, clinically silent endocrine abnormalities and an increased risk of infection. The incidence of overall infections (82% vs. 80%), bacterial infections (35% vs. 17%) and fungal infections (28% vs. 14%) were higher in the everolimus group vs. the AZA group. At 12 months the incidence of viral infections (30% vs. 29%), and specifically, CMV infections (9% vs. 12%), was similar in the everolimus and AZA groups, respectively. The incidence of malignancies was low, and did not show a difference between the everolimus vs. AZA groups (7% vs. 5%).

**Use of Everolimus in Liver Transplantation**

***Efficacy Summary***

In study B158 with 119 *de novo* liver transplant patients, the incidence of the composite endpoint (biopsy-proven and treated acute rejection, graft loss, death or lost to follow-up at month 12) was similar for all 3 doses of everolimus (1, 2 and 3 mg/day) and placebo (50%, 43%, 42% and 47%, respectively). No between-group differences were observed for the individual components of this composite endpoint, although there was a trend towards fewer acute rejection episodes and fewer deaths in the everolimus 2 and 4 mg/day groups.

In 119 *de novo* liver transplant patients, the incidence of the composite endpoint (biopsy-proven and treated acute rejection, graft loss, death or lost to follow-up) was similar for all 3 doses of everolimus (1, 2 and 4 mg/day) and placebo at month 12 and for the 3 doses of everolimus at 36 months. There were no dose-related or statistically significant differences between treatment groups in the incidence rate of efficacy failure or its single components. All graft losses and most deaths were secondary to typical post-transplant complications, and none of them were considered to be associated with the study medication. Most efficacy-related events occurred before 12 months. No between-group differences were observed for the individual components of this composite endpoint, although there was a trend towards fewer acute rejection episodes and fewer deaths in the everolimus 2 and 4 mg/day groups though 36 months. Pharmacokinetic modeling, consistent with that observed in renal and cardiac transplant studies suggests that the risk of acute rejection is associated with the trough levels of everolimus similar to other solid transplant organs. Trough levels of everolimus > 3 ng/ml had numerically lower events of rejection within the first year compared to placebo.

***Safety Summary***

In study B158 with *de novo* liver transplant recipients, more patients in the fixed dose everolimus groups, used with standard doses of cyclosporine, than in the placebo group discontinued study medication due to AEs. The incidence of nonfatal SAEs was slightly higher in the everolimus treated patients. More patients in the everolimus 2 and 4 mg/day groups showed notably high total cholesterol levels. More patients reported hypertriglyceridemia as an AE in the everolimus 2 and 4 mg/day groups than in the other groups. Acute renal failure occurred more frequently in the everolimus 2 and 4 mg/day groups. The incidence of hepatic arterial thrombosis (HAT) was low in this study (2 of 89 patients in the everolimus groups and 1 of 30 patients in the placebo group).

**Summary and Conclusions of Novartis' Clinical Data on Everolimus**

In summary, Novartis clinical trials demonstrate the safety of therapeutic levels of everolimus greater than 3.0 ng/ml. The blood levels of everolimus achieved with oral doses used in clinical trials of organ transplant rejection greatly exceed the *in vivo* systemic exposure with the implantation of XIENCE V product.

### 5.4 Packaging Information

Both the XIENCE V RX and OTW systems have a protective sheath that covers the stent/balloon area and is inserted into a dispenser coil. The dispenser coil is placed into an inner header bag, which is heat sealed and given a product label. The header bags are placed into a corrugated shipping box and ethylene oxide (EtO) sterilized.

Post sterilization, each header bag is placed inside an outer foil pouch. First, the foil pouch is purged of ambient air and filled with an inert gas. Next, the pouch is heat sealed, labeled, and placed inside a labeled carton. Individual products in a carton are placed into suitable corrugated boxes designed to protect the packaged product from damage during transit.

# Handbook of Drug-Eluting Stents

Patrick W. Serruys
Anthony H. Gershlick
Editors

Taylor & Francis
Taylor & Francis Group

# Contents


List of contributors xi

Preface xix

**PART I**
**BACKGROUND AND INTRODUCTION** **1**

1. Restenosis following percutaneous coronary interventions: a clinical problem 3
   *Eugenia Nikolsky, Roxana Mehran, Dale T Ashby, George D Dangas, Alexandra J Lansky, Gregg W Stone, Jeffrey W Moses, and Martin B Leon*

2. Histopathology of restenosis 15
   *Andrew J Carter and Philip Tsao*

3. Cellular mechanisms of restenosis: conventional dogma and novel theory 25
   *Robert S Schwartz*

4. Molecular basis of restenosis and potential therapeutic targets 39
   *Yiming Yang, Andrew R Marks, and Steven O Marx*

5. Principles of continuum pharmacokinetics in stent-based drug elution 47
   *Chao-Wei Hwang and Elazer R Edelman*

6. Importance of the toxic/therapeutic window 57
   *Arun Kuchela and Campbell Rogers*

7. Drug delivery coatings 65
   *Michael Kuehler and Ivan De Scheerder*

8. The importance of the drug platform: coated, uncoated, sleeves, and new concepts 75
   *Dougal R McClean and Frank Litvack*

**PART II**
**DRUG–STENT PROGRAMS** 85

9. Rapamycin structure and mechanism of action 87
*Steven O Marx and Andrew R Marks*

10. Sirolimus-coated stent: preclinical studies 93
*Andrew J Carter, Gregory A Kopia, and Robert Falotico*

11. Nonrandomized registries for de novo lesions (FIM) and in-stent restenosis 103
*J Eduardo Sousa, Alexandre C Abizaid, Marco A Costa, Amanda GMR Sousa, Fausto Feres, and Ibraim Pinto*

12. The RAVEL trial 109
*Marie-Claude Morice*

13. The SIRIUS, E-SIRIUS, and C-SIRIUS trials 121
*Michael Schlüter and Joachim Schofer*

14. Sirolimus-eluting coronary stent in high-risk patients with complex lesions: subset data from controlled clinical trials and registries 133
*Pedro A Lemos*

15. Local vascular delivery of paclitaxel: background, mechanisms, and pharmacodynamic properties 145
*Mary E Russell, Edmund A Bermudez, and Simona Cipra*

16. Preclinical experience with the paclitaxel-eluting stent: the Boston Scientific Program 153
*Douglas E Drachman and Campbell Rogers*

17. The Quanam drug-eluting stent and the SCORE trial 157
*Eberhard Grube*

18. Initial experiences with paclitaxel-eluting stents for treatment of de novo as well as in-stent restenotic lesions: TAXUS I and TAXUS III 165
*Eberhard Grube and Patrick W Serruys*

19. The Boston Scientific Taxus trials 173
85 *Antonio Colombo and Gregg W Stone*

87 20. Local delivery of paclitaxel as a stent coating: biology and clinical
implications 185
*Alan W Heldman*

93

21. Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) 191
*Seung-Jung Park*

103 22. PATENCY Pilot study: a negative trial, in context 201
*Alan W Heldman*

23. Paclitaxel-eluting stents—the ELUTES trial 205
109 *Neil Swanson and Anthony H Gershlick*

24. Vascular Endothelial Growth Factor (VEGF)-eluting stents 209
121 *Neil Swanson and Anthony H Gershlick*

25. The Millennium Matrix™ Coronary Stent 215
*Rajesh Vaishnav, Devesh Kothwala, and Rohit Chand*

133

26. The Conor drug delivery stent 227
*Joseph Aragon and Frank Litvack*

145 27. Actinomycin-eluting stent for coronary revascularization: a randomized
feasibility and safety study (the ACTION trial) 233
*Patrick W Serruys, John A Ormiston, Muzaffer Degertekin, Kengo Tanabe,
J Eduardo Sousa, Eberhard Grube, Peter den Heijer, Pim de Feyter,*
153 *Pawel Buszman, Albert Schömig, Jean Marco, Lech Polonski, Leif Thuesen,
Andreas M Zeiher, JH Nicholas Bett, Maarten J Suttorp, Helmut D Glogar,
Mark Pitney, Gerard T Wilkins, Robert Whitbourn, Susan Veldhof,*
157 *Karine Miquel, Rachel Johnson, and Renu Virmani*

28. Guidant deliver II study: prospective, nonrandomized, multicenter evaluation of
the ACHIEVE™ paclitaxel-eluting coronary stent system in the treatment of lesions
165 with high risk of revascularization due to restenosis 243
*Eberhard Grube*

29. Guidant deliver clinical trial: prospective, randomized, single-blinded, parallel-group (two-arm), multicenter, clinical evaluation of the RX ACHIEVE™ drug-eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions 245
*William O'Neill and William D Knopf*

30. Batimastat: mode of action, preclinical, and clinical studies 247
*Ivan De Scheerder, Xiaoshun Liu, Bernard Chevalier, Guy LeClerc, and Anthony Collias*

31. The prevention and treatment of in-stent restenosis—the current challenge for coronary intervention 261
*Sandra E Burke and Tony M Chou*

32. Dexamethasone: mode of action, preclinical, and clinical studies 273
*Ivan De Scheerder, Xiaoshun Liu, Yanming Huang, Eric Verbeken, Joseph Dens, Walter Desmet, and Jan Piessens*

33. 17β-estradiol-eluting stents—a potential therapy in the prevention of restenosis 285
*Gishel New, Nicholas Kipshidze, Alexandre C Abizaid, and Antonio Colombo*

34. An advanced antisense (AVI-4126) for local and stent-based delivery for prevention of restenosis after PCI (current status and future developments) 295
*Nicholas Kipshidze, Jeffrey W Moses, Patrick Iversen, Patrick W Serruys, and Martin B Leon*

35. The Endeavor Drug-Eluting Stent program 305
*Ian T Meredith*

36. Terumo statin releasing stent (preclinical results) 313
*Kengo Tanabe, Haruo Ishiyama, Willem J van der Giessen, and Patrick W Serruys*

37. Duraflex™ Drug-Eluting Coronary Stent System 323
*Alexandre C Abizaid, Vinayak D Bhat, Andrew J Carter, Guy LeClerc, Lynn Morrison, and John Yan*

38. Genous™ Bio-engineered R stent™: development and the HEALING clinical evaluations 329
*Stephen Rowland, Robert Cottone, H Richard Davis, Margaret Yoklavich, and Michael JB Kutryk*



39. E
E
40. C
A
*Index*

245
247
261
273
285
295
305
313
323
329

39. Everolimus-eluting stents 341
*Eberhard Grube and Lutz Buellesfeld*

40. Contemporary state of drug-eluting stents 349
*Andrew TL Ong, Pedro A Lemos, Anthony H Gershlick, and Patrick W Serruys*

*Index* 365

tely 500
ned as

llow-up

# 30. Batimastat: mode of action, preclinical, and clinical studies

Ivan De Scheerder, Xiaoshun Liu, Bernard Chevalier, Guy LeClerc, and Anthony Collias

## CELL MIGRATION: A TARGET FOR THE CONTROL OF RESTENOSIS

It has long been considered that restenosis following balloon angioplasty is the result of the formation of excessive neointima. More recently, both animal and human studies have shown that constrictive arterial remodeling is the major determinant of restenosis after balloon angioplasty, and it is responsible for up to 70% of late lumen loss. Arterial remodeling in this context means a structural change of the vessel wall, where reorganization of cells and matrix at sites of injury leads to decreased lumen diameter. At the heart of this remodeling process is the degradation of the extracellular matrix by a group of enzymes known as matrix metalloproteinases (MMPs), secreted predominately by vascular smooth muscle cells (VSMCs) but also macrophages and monocytes.

## THE MMPs

The MMPs are a family of zinc-dependent neutral endopeptidases that share structural domains but differ in substrate specificity, cellular sources, and inductivity (see Table 30.1). All the MMPs are important for the remodeling of the extracellular matrix and share the following functional features: (1) they degrade extracellular matrix components, including fibronectin, collagen, elastin, proteoglycans, and laminin; (2) they are secreted in a latent proform and require activation for proteolytic activity; (3) they contain zinc at their active site and they need calcium for stability; (4) they function at neutral pH; and (5) they are inhibited by specific tissue inhibitors of metalloproteinases (TIMPs).

The activity of the MMPs is controlled at the transcriptional level, by activation of the latent proenzymes, and by their endogenous inhibitors, the TIMPs. While the low level expression of most MMPs is generally found in normal adult tissue, it is upregulated during certain physiological and pathological remodeling processes. Induction or stimulation at transcriptional level is mediated by a variety of inflammatory cytokines, hormones, and growth factors, such as IL-1, IL-6, TNF$\alpha$, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and CD40. Binding of these stimulatory ligands to their receptors triggers a cascade of intracellular reactions that are mediated through at least three different classes of mitogen-activated protein (MAP) kinases: extracellular signal-regulated kinase, stress-activated protein kinase/Jun N-terminal kinases, and p38. Activation of these kinases culminates in the activation of a nuclear AP-1 transcription factor, which binds to the AP-1 *cis* element and activates the transcription of corresponding MMP gene. Other factors such as corticosteroids, retinoic acid, heparin, and IL-4 have been demonstrated to inhibit MMP gene expression [1].

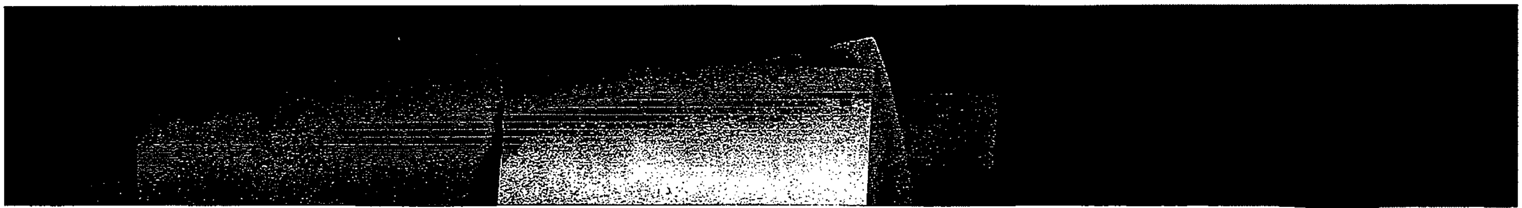




**Table 30.1 MMP family (Creemers EEJM. et al., 2001)**

| Enzyme | MMP Classification | Substrate(s) |
|---|---|---|
| Collagenases | | |
| Interstitial collagenase | MMP-1 | Collagen types I, II, III, VII, and X, gelatin, entactin, aggrecan |
| Neutrophil collagenase | MMP-8 | Collagen types I, II, and III, aggrecan |
| Collagenase-3 | MMP-13 | Collagen types I, II, and III, gelatin, fibronectin, laminins, tenascin |
| Collagenase-4 | MMP-18 | Not known |
| Gelatinases | | |
| Gelatinase A | MMP-2 | Collagen types I, IV, V, and X, fibronectin, laminins, aggrecan, tenascin-C, vitronectin |
| Gelatinase B | MMP-9 | Collagen types IV, V, XIV, aggrecan, elastin, entactin, vitronectin |
| Stromelysins | | |
| Stromelysin 1 | MMP-3 | Collagen types III, IV, IX, and X, gelatin, fibronectin, laminins, tenascin-C, vitronectin |
| Stromelysin 2 | MMP-10 | Collagen IV, fibronectin, aggrecan |
| Stromelysin 3 | MMP-11 | Collagen IV, fibronectin, aggrecan, laminins, gelatin |
| Membrane-type (MT-MMPs) | | |
| MT1-MMP | MMP-14 | Collagen types I, II, and III, fibronectin, laminins, vitronectin, proteoglycans; activates proMMP-2 and proMMP-13 |
| MT2-MMP | MMP-15 | Activates proMMP-2 |
| MT3-MMP | MMP-16 | Activates proMMP-2 |
| MT4-MMP | MMP-17 | Not known |
| MT5-MMP | MMP-24 | Activates proMMP-2 |
| MT6-MMP | MMP-25 | Not known |
| Nonclassified MMPs | | |
| Matrilysins | MMP-7 | Gelatin, fibronectin, laminins, elastin, collagen IV, vitronectin, tenascin-C, aggrecan |
| Metalloelastase | MMP-12 | Elastin |
| Unnamed | MMP-19 | Not known |
| Enamelysin | MMP-20 | Aggrecan |
| | MMP-23 | Not known |
| Endometase | MMP-26 | Not known |

## THE ROLE OF MMPs IN RESTENOSIS

Although the precise role of MMPs in inducing VSMC migration is not fully understood, there are multiple proposed mechanisms of action, which include the removal of physical restraints by the severing of cell–matrix contacts via integrins or cell–cell contacts via adherins. Additionally, contact with interstitial matrix components may be facilitated and migration may be stimulated through exposure of cryptic extracellular matrix sites, production of extracellular matrix fragments and the release of matrix or cell-bound growth factors [2]. Other recent studies also demonstrate that MMP activity is required for lymphocyte transmigration across endothelial venules into lymph nodes, providing some evidence for the concept that MMPs are important players in transendothelial migration [3].

Coronary angioplasty inevitably produces a mechanical injury to the vessel. Damage to the endothelia is thought to trigger phenotypic modulation of medial VSMCs, changing them from a normal contractile (differentiated) phenotype to a synthetic (proliferative) state. To enable VSMC migration, remodeling of the basement membrane and the interstitial collagenous matrix that maintains VSMCs in a quiescent state must occur. Intimal thickening ensues because of the migration of medial

VSMCs to the intima, where they proliferate and secrete extracellular matrix proteins. This is supported by studies on aortic explants [4], in rat carotid arteries [5], and in human saphenous vein [2], which have shown that mechanical injury stimulates the production of MMPs. More specifically, remodeling following injury in the rat carotid artery model has been shown to be associated with increased expression of the gelatinases MMP-9 and MMP-2, and subsequently with increased migration and proliferation of VSMCs [6]. Furthermore, the response to arterial balloon injury involves MMP-dependent VSMC migration and can be attenuated by TIMP-1 expression. In vivo arterial gene transfer of TIMP-1 attenuates neointimal hyperplasia after vascular injury, with a marked reduction in VSMC migration but without altering proliferation [7]. These results confirm that the balance of MMPs/TIMPs is important, and support the supposition that targeting it can be a powerful approach to control the migratory capabilities of the cells and, consequently, control restenosis following balloon angioplasty and stenting.

## BATIMASTAT: MODE OF ACTION

Batimastat, (4-N-hydroxyamino)-2R-isobutyl-3s-(thiopen-2-ylthiomethyl)-succinyl-l-phenylalanin-*n*-methylamide, was originally developed by British Biotech Pharmaceuticals Ltd as a broad-spectrum metalloproteinase inhibitor (MMPI). It is a low molecular weight (478) peptide mimetic comprised of the peptide residues found on one side of a principal cleavage site in type I collagen, containing a hydroxamate group (Figure 30.1). This group chelates a zinc atom in the active site of the MMP, inhibiting the enzyme reversibly.

The three classes of MMP (collagenases, stromelysins, and gelatinases) are potently inhibited by Batimastat, with an $IC_{50}$ in the low nanomolar range. It shows no activity against unrelated metalloproteinases such as

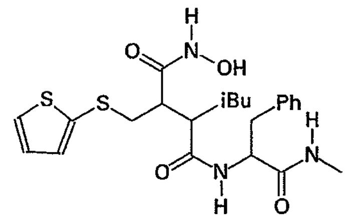


**Figure 30.1**

Chemical structure of Batimastat.

enkephalinase or angiotensin converting enzyme. These enzymes are critical in matrix degradation and invasion by cancer cells (development of cancer metastasis), in the process of arterial remodeling after injury, in cytokine receptor shedding and in the development of restenosis after coronary angioplasty.

Batimastat has been shown to suppress injury-induced phosphorylation of MAP kinase ERK1/ERK2, which is an important signaling pathway of the injury-induced activation of the cells, both restraining the phenotypic modulation and suppressing injury-induced DNA synthesis and migration in VSMC cultures [8]. In an in vitro model of baboon aortic medial explants, Batimastat was able to inhibit basal cell migration [9], and more specifically in a rat carotid model, inhibited intimal thickening after balloon injury by decreasing VSMC migration and proliferation [10]. A study in Yucatan minipigs showed Batimastat significantly reduced late lumen loss after balloon angioplasty by inhibition of constrictive arterial remodeling [11]. In studies with other MMPIs, marimastat was also shown to affect the arterial wall following balloon angioplasty in favor of neutral and expansive remodeling [12], while in a double-balloon injury model in rabbits, the broad spectrum MMPI GM6001 was shown to reduce intimal cross-sectional area and collagen content by 40% in stented arteries [13]. These data help support the rationale for the

use of a Batimastat-loaded stent to help reduce the restenotic response of the artery after stenting.

## PRECLINICAL ASSESSMENT OF THE BIO*DIVYSIO* BATIMASTAT STENT

A total of five animal studies, ranging from 5 days to 3 months implantation, have been conducted with the Batimastat-loaded Bio*divYsio* Stent. A summary of the preclinical studies is shown in Table 30.2. In all the animal studies, Batimastat was loaded on either the Bio*divYsio* AS or OC Stents since these stents are more applicable to the vessel size of the selected animal models.

In all cases stent implantation oversizing (i.e. balloon/artery ratio >1) was performed to cause an injury to the artery wall that would result in neointimal formation resembling that occurring in stented human coronary arteries. Angiographic data were obtained before and just after implantation of the stent and were compared to that obtained at the end of each study. In some studies the performance of the Batimastat doses were evaluated by histological measurement of neointimal hyperplasia formation and lumen area changes and compared to the performance of the nondrug loaded stents as a control. Appropriate antiplatelet therapy was administered according to the type of study performed.

## SHORT-TERM STUDIES

The 5-day farm swine study evaluated the subacute safety and re-endothelialization of two doses of Batimastat $0.30 \pm 0.13\ \mu g/mm^2$ (CTD) and $1.43 \pm 0.20\ \mu g/mm^2$ (>CTD) delivered from the 15 mm Bio*divYsio* Batimastat OC Stent compared to Bio*divYsio* PC-coated OC Stents without Batimastat (control). All stents were implanted without problems and there were no deaths during the 5-day follow-up period. All animals were sacrificed at 5 days. The SEM analysis was performed

**Table 30.2 Preclinical study summary**

| Study | Implantation period | Stent | Total dose/µg Batimastat per mm² of stent (number of stents implanted) Control | <CTD[a] | CTD[b] | >CTD[c] | Animals |
|---|---|---|---|---|---|---|---|
| Short term | 5 day | Preloaded 15 mm OC Stent | 0 (6) | | 0.30 (7) | 1.39 (7) | 10 farm swine |
| | 1 month | Non-preloaded OC Stent | 0 (8) | | 0.30 (8) | 1.09 (8) | 12 farm swine |
| | 1 month | Preloaded AS Stent | 0 (10) | | 0.30 (10) | | 10 farm swine |
| Short and long term | 1 and 3 months | Preloaded AS Stent | 0 (15) | 0.03 (17) | 0.30 (30) | | 26 Yucatan minipigs |
| Pharmacokinetic | 24 hours and 1 month | Preloaded OC Stent | | 0.37 (12) (1 µCi radiolabeled Batimastat $^{14}C$ per stent) | | | 9 New Zealand white rabbits |

CTD—Clinical trial dose specification established for larger vessel clinical trials (i.e., BRILLIANT EU) and the actual measured dose for the animal study dose is within this CTD range.
[a]These samples were produced using a less concentrated drug solution to achieve a lower than CTD.
[b]The manufacturing range during the preparation of these stents was 0.30 µg Batimastat per mm² of stent surface area.
[c]These samples were prepared as for CTD stents; additional Batimastat was added by pipette to increase the dose.

on all arteries from a total of three animals selected randomly. The rate and extent of endothelialization of the stent struts and the presence of any cellular/biological debris within the stented segment was assessed, and the results showed that Batimastat did not interfere with the process of stent endothelialization, the degree of cell coverage being similar to that of the control stent. A continuous and confluent layer of endothelial cells was observed on the inner surface of the stented vessel segments for all stents including control stents. The high degree of endothelial cell coverage over the inner surface of the vessel in each of these cases is consistent with previous observations made by Whelan et al. [14]. Some white cells and mural thrombus were also observed. It can be concluded that Batimastat loaded onto the Bio*divYsio* stent at the CTD or >CTD dose does not affect the in vivo endothelialization process at 5 days in comparison to the control (Figure 30.2).

Offline Quantitative Coronary Angioplasty (QCA) analysis of all stented vessel segments was also performed, and indicated that there were no stent thromboses nor significant differences in percentage stenosis between the control group (3.8%) versus CTD (4.8%) and >CTD (4.4%). The fact that both the controls and the Batimastat-loaded stents showed a low stenosis rate demonstrates that the processes of migration, proliferation, and remodeling were in their early stages (Figure 30.3) [15].

**Figure 30.2**

SEM showing continuous endothelial cell coverage of the stent struts after 5-day implantation (CTD dose Bio*divYsio* Batimastat Stent).

The 1-month farm swine studies evaluated safety following implantation of two doses of Batimastat loaded on the 18 mm Bio*divYsio* stent in comparison to control stent without Batimastat. Two Batimastat doses were evaluated as described in Table 30.2. No deaths occurred during the implantation procedure and no subacute death or stent thrombosis was observed during the follow-up period. Histological examination confirmed that all the vessels were patent, without the presence of thrombus in the vessel lumen. All sections showed stent struts to be completely covered, leading to a smooth endoluminal surface. There was no excessive inflammatory response at stent struts in Bio*divYsio* Batimastat-treated sections compared to the control sections. Medial and adventitial layers appeared similar in all three groups. The perivascular nerve fibers, the adipose tissue, and adjacent myocardium appeared normal in control and Bio*divYsio* Batimastat-treated sections. Therefore these studies demonstrated that the Bio*divYsio* Batimastat stent at CTD and >CTD was well tolerated upto 28 days.

The study of the pharmacokinetics of release of Batimastat from the Bio*divYsio* Batimastat Stent was initiated to investigate the deposition of the drug from the stent in the arterial wall and major organs. These studies used the well-established New Zealand white rabbit model where $^{14}C$ Batimastat-loaded Bio*divYsio* OC Stents, at a dose of 0.37 $\mu g/mm^2$, were placed in the left and right iliac arteries and levels of Batimastat deposited in the iliac arteries and solid organs were measured 28 days after stent implantation.

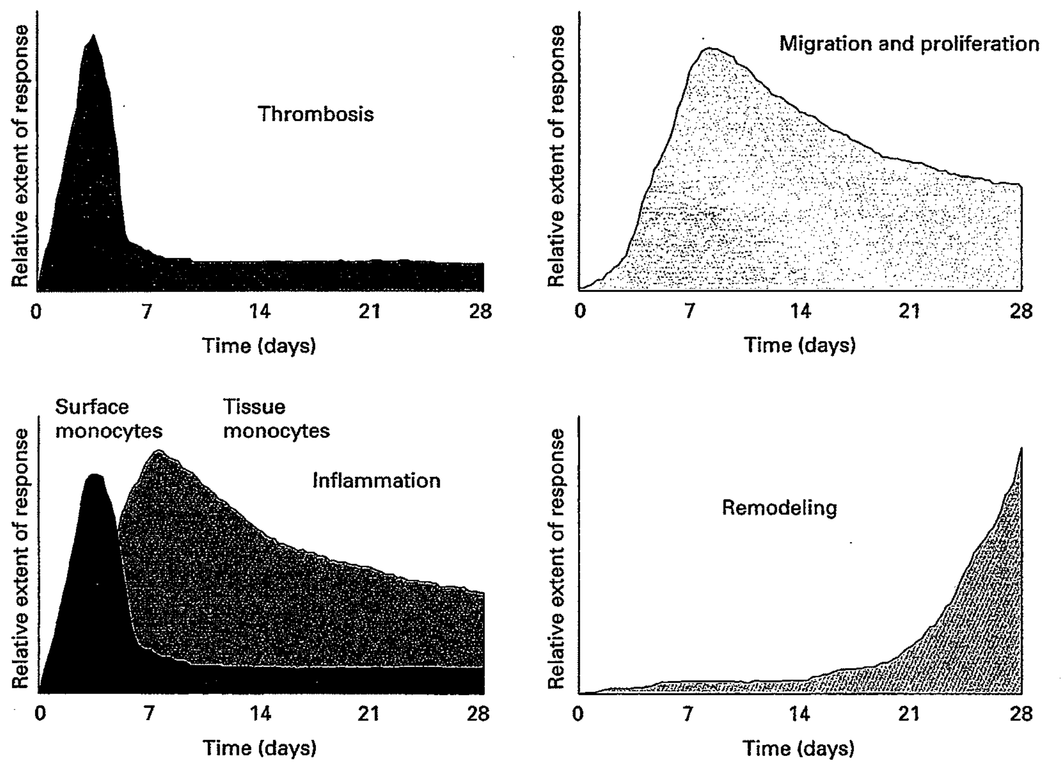



**Figure 30.3**

The phases and their timing in the restenosis process.

A total of 18 Bio*divYsio* Batimastat OC Stents were implanted in nine rabbits. Three of the nine rabbits were implanted for only 1 day while the remaining six rabbits were implanted for 28 days. The study demonstrated the reproducible release and deposition of drug from the Bio*divYsio* Batimastat stent. Release was reproducible at all time points and was first order. Within the first 24 hours, 72.9 ± 4.0% was released and the bulk of loaded drug (94%) was eluted 28 days postimplantation. Drug released from each stent is primarily localized to the 15 mm long-stented region, and to a lesser degree the adjacent adventitia and regions immediately proximal and distal to the stent. The data follow the expected patterns of release and deposition and indicate that there is unlikely to be a long-term issue of residual drug within the artery wall after release has terminated. Very little of the drug was found in the distal organs (brain, liver, kidney, spleen, carotid artery, gonad, heart, lung, and intestine), the numbers obtained being so low that they could be considered as undetectable.

## LONG-TERM STUDIES

The long-term (3 months) safety study was carried out on Yucatan minipigs using two doses of Batimastat loaded on the 15 mm



**Table 30.**
**analysis**

Injury score
% In-stent st
Vessel area (
Lumen area
Neointimal
Intimal/me
Thrombus p

Bio*divYsio* stent witl Table 30.2 vessel lum area, abse graphic pe The QCA a follow-up At 3 mo 20% and respective of the trea uation sh effects of the contro could be intensity c matory ce different f

CLINICA

One clini evaluate t Stent in c The BR Restenosi drug deli prospecti single pil cardiovas

feration

28

28

ease and
unlikely
g within
minated.
he distal
carotid
ine), the
hat they

ıdy was
ing two
15 mm

**Table 30.3 Month QCA and histology analysis**

| | Control | <CTD | CTD |
|---|---|---|---|
| Injury score | 1.6 | 1.5 | 1.3 |
| % In-stent stenosis | 34.10 | 27.20 | 22.50 |
| Vessel area (mm$^2$) | 9.4 | 9.9 | 9.4 |
| Lumen area (mm$^2$) | 3.2 | 3.3 | 3.6 |
| Neointimal area (mm$^2$) | 3.9 | 3.9 | 3.3 |
| Intimal/medial ratio | 0.74 | 0.72 | 0.74 |
| Thrombus present | No | No | No |

Bio*divYsio* stent in comparison to a control stent without Batimastat, as outlined in Table 30.2. The evaluation criteria included vessel lumen area, neointimal thickness and area, absence/presence of thrombus, angiographic percentage stenosis, and lumen loss. The QCA and histological analysis at 3 months follow-up are presented in Table 30.3.

At 3 months, the stenosis was reduced by 20% and 34% in the <CTD and CTD dose, respectively. These data show a trend in favor of the treatment groups. Histopathology evaluation showed that there were no adverse effects of the drug-loaded stent compared to the controls, and no deleterious phenomenon could be attributed to the drug tested. The intensity of fibrosis, hemorrhages, and inflammatory cell infiltration were not significantly different from the control group at 3 months.

## CLINICAL STUDIES WITH THE BIO*DIVYSIO* BATIMASTAT STENT

One clinical registry has been performed to evaluate the safety of the Bio*divYsio* Batimastat Stent in countries outside the United States.

The BRILLIANT-EU (Batimastat (BB94) anti-Restenosis trIaL utiLizIng the Bio*divYsio* locAl drug delivery PC-steNT) was a multicenter, prospective, noncontroled, European-based single pilot trial performed at 8 interventional cardiovascular sites in Belgium, 10 sites in France, and 2 sites in the Netherlands (Figure 30.4). The primary purpose of this multicenter, prospective registry was to evaluate the acute safety and effectiveness of the Bio*divYsio* Batimastat OC Stent (2.0 μg Batimastat/mm$^2$ of stent surface area) in patients with a single, de novo lesion ≤25.0 mm in length, requiring endovascular stenting following percutaneous transluminal coronary angioplasty (PTCA). The primary objective was to evaluate the occurrence of MACE (death, recurrent myocardial infarction, or clinically-driven target lesion revascularization) 30 days post-procedure. The secondary objectives were to evaluate the binary restenosis, incidence of (sub)acute stent thrombosis (SAT) at 30 days follow-up, MACE at 6 and 12 months, and the QCA endpoints at 6 months. This study was designed to allow a comparison with the patient population and the results of a larger randomized DISTINCT (Bio*divYsio* stent in controlled clinical trial) study previously conducted in the United States.

## STUDY DESIGN

A total of 173 Patients (134 male and 39 female) symptomatic with stable angina pectoris (Canadian Cardiovascular Society 1, 2, 3, or 4) or unstable angina pectoris with documented ischemia (Braunwald Class IB-C, IIB-C, or IIIB-C) or documented ischemia with a single de novo lesion in a coronary artery suitable for treatment with a single Bio*divYsio* DD OC coated coronary stent preloaded with Batimastat of 11, 15, 18, 22, or 28 mm length by 3.0, 3.5, or 4.0 mm diameter were included in the study, providing they met the selection criteria.

All patients were required to agree to a 6-month clinical and angiographic follow-up and had to be over 18 years old. The reference vessel diameter of the treated lesion was visually estimated >2.75 and <3.5 mm in diameter, target lesion stenosis >50% and <100%.

BRILLIANT-EU

Batimastat (BB94)anti-Restenosis trIaL utiLizIng the Bio*divYsio* locAl drug Delivery PC-steNT

| | |
|---|---|
| Purpose | To evaluate the acute safety and effectiveness of the Bio*divYsio* Batimastat Stent |
| Structure | Multicenter, prospective, noncontrolled study |
| Study devices | 11, 15, 18, 22, and 28mm Bio*divYsio* Batimastat Stents in diameters of 3.0, 3.5, and 4.0 mm |
| Batimastat dose | 0.30 µg Batimastat per mm$^2$ |
| Enrollment | European study of 150 patients |
| Clinical sites | 22 sites in France, Belgium, and Holland. |
| Clinical follow-up | All patients will undergo clinical follow-up at 30 days, 6 and, 12 months post procedure |
| Angiographic follow-up | Patients will undergo angiographic follow-up at 6 months post procedure |
| Primary endpoint | MACE (death, recurrent myocardial infarction, or clinically-driven target lesion revascularization) at 30 days. |
| Secondary endpoints | Binary restenosis at 6 months follow-up (defined as ≥50% diameter stenosis by QCA) Quantitative coronary angiography endpoints including late loss, loss index, late absolute MLD at 6 months incidence of (sub)acute stent thrombosis (SAT) to 30 day follow-up MACE at 6 months and 12 months |
| PI's | Dr de Scheerder—UH Gasthuisberg, Leuven<br>Dr Chevalier—Centre Cardiologique du Nord, Paris |

**Figure 30.4**

Structure of BRILLIANT-EU.

Noncalcified lesions, de novo lesions within a native coronary artery, ≤25 mm long, requiring one appropriately sized Bio*divYsio* Batimastat OC Stent were included.

The following patient categories were excluded from the study: patients with ostial and bifurcation lesions, left ventricular ejection fraction <30%, known hypersensitivity or contraindication to aspirin or stainless steel, or a sensitivity to contrast dye, allergy to heparin or ticlopidine.

The ethics committee at each center approved the protocol. The consent form or modification based on local independent ethics committee recommendations was completed by all enrolled subjects and signed by the operating physician.

## MEDICATION

All patients were premedicated with acetyl salicylic acid (ASA) (160 mg/d) orally. Oral clopidogrel 300 mg or ticlopidine 500 mg was given before PTCA. Heparin (100 U/kg) after insertion of the arterial sheath was weight adjusted and administered as needed to maintain an activated clotting time (ACT) of approximately 250–300 seconds (If a GB IIb/IIIa blocker is used, an ACT of 150–200 seconds suffices). Intracoronary nitroglycerin 50–200 µg was administered immediately prior to baseline angiography, post-stent deployment, and after final post-dilatation angiography. Aspirin

was continued indefinitely and clopidogrel 75 mg or ticlopidine (250 mg/d) was prescribed for 28 days in all cases.

## QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

Pre-procedural, post-procedural, and at 6-month follow-up angiography was performed in at least two orthogonal projections after intracoronary injection of nitrates. Quantitative analyses were performed by an independent core laboratory (Brigham and Women's, Boston, MA). Reference vessel diameter (RVD), MLD, and degree of stenosis (as percentage of diameter) were measured before dilatation, at the end of the procedure, and at a 6-month follow-up. Restenosis was defined as > 50% diameter stenosis at follow-up. Late loss was defined as MLD after the procedure minus MLD at follow-up.

## CLINICAL FOLLOW-UP

All patients were asked to return to the investigative site for a clinical visit 4 weeks ±1 week post-procedure to repeat clinical labs and monitor acute clinical events. All patients were contacted by telephone by the investigative site at 3 months ±1 week for a safety evaluation. All subjects were required to return to the investigative site for a repeat coronary angiography whether they were experiencing symptoms or not. If a patient had a positive exercise stress test at any time upto and including his required follow-up, a repeat angiogram was performed.

## DEFINITIONS AND STATISTICS

Safety Analysis patient set was defined as all patients who received the Bio*divYsio* Batimastat OC Stent. Per Protocol Analysis patient set was defined as all patients in the Safety Analysis set who did not deviate from the protocol. Categorical variables were summarized using counts and percentages. Continuous variables were summarized using mean, standard deviation (SD), minimum and maximum, and median for variable not showing a normal distribution. For comparison of subgroups, the unpaired two-tailed student's *t*-test was used. Results were considered statistically significant at $p < 0.05$.

## RESULTS

### DEMOGRAPHIC CHARACTERISTICS, PROCEDURAL AND IN-HOSPITAL OUTCOMES

The baseline clinical and angiographic characteristics are summarized in Table 30.4. In total, 173 patients were enrolled in the study and had at least one study stent implanted. Nine patients (5%) were excluded from the Per Protocol Analysis, among which six violated the inclusion/exclusion criteria for the study and four (one violated the inclusion/exclusion) had a second stent placed in the study vessel. The mean age was 61 with a range from 34 to 83 years. Hypercholesterolemia (62%), hypertension (46%), and family coronary history (43%) were the most frequently reported risk factors. The majority of patients (69%) had one diseased vessel and the mean left ventricular ejection fraction was 67%. Fifty-nine patients (34%) had experienced a previous myocardial infaution MI, 22 patients (13%) had undergone previous PTCA, and 4 patients (2%) had undergone previous CABG. At preprocedural evaluation, 100 patients (58%) had unstable angina pectoris (including Class 4), 56 patients (32%) patients had stable angina (Class 1, 2, 3), and 17 patients (10%) had silent ischemia.

The most frequent location of the target lesion was the mid-left anterior descending vessel

**Table 30.4 Baseline clinical characteristics**

| | BRILLIANT-EU $n = 173$ ($n$%) |
|---|---|
| Male | 134(77) |
| Mean age (years) | 60.6 ± 10.6(34–83) |
| Risk factors | |
| Family history CHD | 74(43) |
| Hypercholesterolemia | 108(62) |
| Hypertension | 79(46) |
| Peripheral vascular disease | 19(11) |
| Previous stroke | 10(6) |
| Diabetes | 23(13) |
| Current smokers | 55(32) |
| Ex-smokers | 67(39) |
| History of | |
| Previous MI | 59(34) |
| Previous PTCA | 22(13) |
| Previous CABG | 4(2) |
| Left ventricular ejection fraction | 67.0±11.6(30–93) |
| Angina status | |
| Stable angina | 62(36) |
| Unstable angina | 94(54) |
| Silent ischemia | 17(10) |
| Number of diseased vessels | |
| 1 vessel | 119(69) |
| 2 vessels | 36(21) |
| 3 vessels or more | 18(10) |
| Target vessels | |
| LAD | 77(45) |
| RCA | 60(35) |
| LCX | 32(18) |
| Ramus | 4(2) |
| AHA/ACC classification[a] | |
| A | 32(19) |
| B1 | 86(50) |
| B2 | 44(25) |
| C | 11(6) |
| Lesion length (mm) | 11.5±5.0 (4–25) |

Values are mean ± SD or $n$ (%); LAD indicates left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery.
[a]According to AHA/ACC classification.

(39 patients, 23%), proximal left descending vessel (37 patients, 21%) and mid-right coronary artery (35 patients, 20%). Mean lesion length was 11.5 ± 5.0 mm (range from 4 to 25 mm). The most commonly recorded target lesion classification was type B1 (86 patients, 50%).

The majority of patients received either a 15 mm stent (71 patients, 41%), an 18 mm stent (38 patients, 22%), or an 11 mm stent (32 patients, 18%). Mean balloon diameter and length were 3.3 and 16.6 mm, respectively. Mean maximum balloon inflation pressure was 13.3 ATM. Delivery balloon rupture occurred in four patients (2%) during the stent placement. The stent was adequately positioned in 170 patients (98%). Three patients (2%) experienced a residual dissection after stent placement. Two patients (1%) experienced three post-procedural in-hospital complications. One experienced a pseudoaneurysm or arteriovenous fistula at arterial access site requiring surgery and blood loss requiring transfusion. One patient experienced hypotension.

There were no MACE resulting from the angioplasty or stenting procedure. Two non Q-wave MI occurred post-procedural during hospitalization. Technical device success, defined as intended stent successfully implanted as the first stent, was achieved in 170 patients (98%). Clinical device success, defined as technical device success in the absence of MACE was achieved in 168 patients (97%). Procedural success, defined as ≥20% reduction in percentage stenosis of the target lesion from immediately prior to intervention to immediately after stent deployment and ≤50% diameter stenosis immediately after stent deployment, using the assigned treatment alone was achieved in 162 patients (94%) of the patients.

## CLINICAL RESULTS

### SHORT-TERM (UP TO 30 DAYS) RESULTS

At the 30-day (± 7days) follow-up, one cardiac death was reported. There were no significant changes in blood parameters either immediately post-procedure or at 30-day follow-up. There were no reports of Q-wave MI, CABG, or repeated angioplasty up to 30 days post-procedure. In addition, there were no reported

cases of SAT. The MACE-free rate at 30 days was 98%.

### THE 6-MONTH FOLLOW-UP

Between 30 days and 6 months post-procedure, 32 MACE were reported (18%), one patient experienced cardiac death (ventricular fibrillation), two patients had non Q-wave MI, and one experienced CABG, and 28 patients underwent target lesion revascularization (TLR) (Table 30.5).

### ANGIOGRAPHIC OUTCOME

Angiographic data were available from 146 patients (Table 30.6). Mean reference vessel diameter (defined as the average of normal segments within 10 mm proximal and distal to the target lesion from two views using QCA) was

**Table 30.5 Ranked major cardiac events (MACE) by descending severity and number of events during 6-month follow-up**

| MACE | BRILLIANT-EU $n$ = 173 (%) | | | | | |
|---|---|---|---|---|---|---|
| | In-hospital $n$ (%) patients | Number of events | Up to 30-day follow-up $n$ (%) patients | Number of events | Up to 6-month follow-up $n$ (%) patients | Number of events |
| Cardiac death | 0(0) | 0 | 1(1) | 1 | 2(1) | 2 |
| Q-wave MI | 0(0) | 0 | 0(0) | 0 | 0(0) | 0 |
| Non-Q-Wave | 2(1) | 2 | 2(1) | 2 | 4(2) | 4 |
| CABG | 0(0) | 0 | 0(0) | 0 | 1(1) | 1 |
| TLR | 0(0) | 0 | 0(0) | 0 | 24(14) | 28 |
| Total MACE | 2(1) | 2 | 3(2) | 3 | 31(18) | 35 |

**Table 30.6 QCA data: comparison between BRILLIANT-EU and DISTINCT**

| | BRILLIANT-EU | DISTINCT | $p$ value |
|---|---|---|---|
| Before procedure | $n$ = 163 | $n$ = 313 | |
| RVD (mm) | 2.91 ± 0.41 | 2.95 ± 0.48 | 0.366 |
| MLD (mm) | 1.01 ± 0.34 | 0.81 ± 0.37 | $p < 0.001$ |
| %DS | 65.20 ± 10.70 | 72.27 ± 11.92 | $p < 0.001$ |
| After procedure | $n$ = 163 | $n$ = 146 | |
| RVD (mm) | 2.99 ± 0.39 | 2.92 ± 0.47 | 0.154 |
| MLD (mm) | 2.50 ± 0.45 | 2.87 ± 0.43 | $p < 0.001$ |
| %DS | 16.54 ± 8.39 | 2.87 ± 12.08 | $p < 0.001$ |
| Acute gain (mm) | 1.81 ± 0.38 | 2.03 ± 0.49 | $p < 0.001$ |
| Follow-up | $n$ = 146 | $n$ = 143 | |
| RVD (mm) | 3.12 ± 2.96 | 2.90 ± 0.45 | 0.380 |
| MLD (mm) | 1.81 ± 0.63 | 1.94 ± 0.67 | 0.090 |
| %DS | 37.65 ± 20.20 | 33.27 ± 20.67 | 0.070 |
| Late loss (mm) | 0.88 ± 0.63 | 0.94 ± 0.61 | 0.412 |
| Loss index | 0.50 ± 0.39 | 0.48 ± 0.33 | 0.639 |
| Binary restenosis rate (%) | 23 | 19.7 | NS |

DS: diameter stenosis. NS: no significant difference.

similar at pre PTCA, post-stent implantation and at 6 months post-procedure (2.91, 2.99, and 3.12 mm respectively). Pre-PTCA, mean MLD in the target lesion was 1.01 ± 0.34 and mean DS of the lesion was 65.20 ± 10.70%. At 6 months, mean MLD was 1.81 ± 0.63 mm and mean DS was 37.65 ± 20.20%. Mean acute gain was 1.81 ± 0.38 mm, mean late loss was 0.88 ± 0.63 and mean loss index was 0.50 ± 0.39. 37 patients (23%) had a significant restenosis at 6-month follow-up angiographic assessment.

## SUMMARY

The data suggest that the Bio*divYsio* Batimastat OC Stent is safe during the period of drug elution from the stent (pharmacokinetic studies have shown that 94% of the Batimastat will have eluted from the PC coating after 1 month). The final 30 days results suggest that the presence of the Batimastat in the coating is not associated with an increased occurrence of MACE or serious adverse events, therefore the Bio*divYsio* Batimastat OC Stent is safe in the short term for use in patients. However, the long-term (6 months) data demonstrate that the Bio*divYsio* Batimastat OC Stent has no additional beneficial effect on restenosis (Table 30.7).

This study was set up to allow a comparison of the patient population and the results with the larger randomized DISTINCT study previously conducted in the United States. The Bio*divYsio* Batimastat OC Stent showed no improvement in the overall unadjudicated MACE (18%) and restenosis (23%) rate at 6 months when compared to the nondrug coated Bio*divYsio* stent used in the DISTINCT study where the reported adjudicated MACE and restenosis rate were 17% and 19.7% respectively. This 6-month follow-up data suggest that the Bio*divYsio* Batimastat OC Stent did not offer the additional benefit over the standard Bio*divYsio* stent (Table 30.7).

**Table 30.7 Six-month clinical follow-up: comparison between BRILLIANT-EU and DISTINCT**

| | BRILLIANT-EU $n = 173$ (%) | DISTINCT $n = 313$ (%) | $p$ value |
|---|---|---|---|
| Cardiac death | 1 | 1 | NS |
| Q-wave MI | 0 | 1 | NS |
| Non-Q-Wave | 2 | 1 | NS |
| TLR | 14 | 11 | NS |
| CABG | 1 | 3 | NS |
| Total MACE | 18 | 17 | NS |

NS: no significant difference.

## CONCLUSIONS

The 5-day, 1-month, and 3-month preclinical data are available for PC Stents loaded with the CTD of Batimastat. Histological analysis showed that the degree of fibrosis, hemorrhages, and inflammatory cell infiltration were not significantly different between the control and CTD stents at all three time points. Data of 5-day and 1-month are available for stents containing greater than three times the CTD. Taken together, these studies demonstrate that the Bio*divYsio* Batimastat Stent is well tolerated in appropriate animal models for the evaluation of restenosis after stent implantation in coronary arteries. The pharmacokinetics release data for the Bio*divYsio* Batimastat Stent follow the expected patterns of release and deposition and indicate that there is unlikely to be a long-term issue of residual drug within the artery wall after release has terminated. The preclinical data at three months with the Bio*divYsio* Batimastat Stent showed a change in the rate of stenosis, where a reduction of 20% and 34% in the <CTD and CTD dose, respectively as measured by QCA was observed. This data showed a trend in favor of the treatment groups.

In addition to the preclinical studies the clinical studies demonstrate that stent-based

deliv
the B
proce
howe
Biodi
loss,

1. Hid
pro
200
2. Jasc
ded
deg
veir
3. Fav
of l
noc
200
4. Jam
and
vas
199
5. Jenl
mer
loca
ball
6. Ben
mig
rial

delivery of Batimastat in coronary artery using the Bio*divYsio* DD stents is a feasible and safe procedure. Results from the BRILLIANT study however did not show a positive effect of the Bio*divYsio* Batimastat OC Stent on TLR, late loss, and binary restenosis.

## REFERENCES


1. Hidalgo M and Eckhardt SG. Development of matrix metalloproteinase inhibitors in cancer therapy. *J Natl Cancer Inst* 2001;93(3):178–93.
2. Jason LJ, Guillaume JJM, Van Eyes GD, et al. Injury induces dedifferentiation of smooth muscle cells and increased matrix-degrading metalloproteinase activity in human saphenous vein. *Arterioscler Thromb Vasc Biol* 2001;21(7):1146–51.
3. Faveeuw C, Preece G, and Ager A. Transendothelial migration of lymphocytes across high endothelial venules into lymph nodes is affected by metalloproteinases. *Immunobiology* 2001;98(3):688–95.
4. James TW, Wagner R, White LA, et al. Induction of collagenase and stromyelysin gene expression by mechanical injury in a vascular smooth muscle-derived cell line. *J Cell Physiol* 1993;157(2):426–37.
5. Jenkins GM, Crow MT, Bilato C, et al. Increased expression of membrane-type matrix metalloproteinase and preferential localitation of matrix metalloproteinase-2 to the neointima of balloon-injured rat carotid arteries. *Circulation* 1998;97:82–90.
6. Bendeck MP, Zempo N, Clowes, AW, et al. Smooth muscle cell migration and matrix metalloproteinase expression after arterial injury in the rat. *Circ Res* 1994;75:539–45.
7. Dollery CM, Humphries SE, McClelland A, et al. Expression of tissue inhibitor of matrix metalloproteinases 1 by use of an adenoviral vector inhibits smooth muscle cell migration and reduces neointimal hyperplasia in the rat model of vascular balloon injury. *Circulation* 1999;99:3199–205.
8. Lovdahl D, Thyberg J, and Hultgardh-Nilsson A. The synthetic metalloproteinase inhibitor batimastat suppresses injury-induced phosphorylation of MAP kinase ERK1/ERK2 and phenotypic modification of arterial smooth muscle cells in vitro. *J Vasc Res* 2000;37(5):345–54.
9. Kenagy RD, Vergel S, Mattsson E, et al. The role of plasminogen, plasminogen activators, and matrix metalloproteinases in primate arterial smooth muscle cell migration. *Arterioscler Thromb Vasc Biol* 1996;16(11):1373–82.
10. Zempo N, Koyama N, Kenagy R D, et al. Regulation of vascular smooth muscle cell migration and proliferation in vitro and in injured rat arteries by a synthetic matrix metalloproteinase inhibitor. *J Vasc Biol* 1996;16(1):28–33.
11. De Smet BJG, De Kleijn D, Hanemaaijer R, et al. Metalloproteinase inhibition reduces constrictive arterial remodeling after balloon angioplasty: a study in the atherosclerotic yucatan micropig. *Circulation* 2000;101:2962–7.
12. Sierevogel MJ, Pasterkamp G, Velema E, et al. Oral matrix metalloproteinase inhibition and arterial remodeling after balloon dilation—an intravascular ultrasound study in the pig. *Circulation* 2001;103:302–7.
13. Li CW, Cantor WJ, Robinson R, et al. Matrix metalloproteinase inhibitor GM6001 selectively reduces intimal hyperplasia and intima collagen in stented but not balloon treated arteries. *Can J Cardiol* 2000;16:suppl. F:143F.
14. Whelan DM, van der Giessen WJ, Krabbendam SC, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. *Heart* 2000;83(3):338–45.
15. Edelman ER and Rogers C. Pathobiologic responses to stenting. *Am J Cardiol* 1998;81(7A):4–6E.

The New England
Journal of Medicine



Volume 331 AUGUST 25, 1994 Number 8

# A COMPARISON OF BALLOON-EXPANDABLE–STENT IMPLANTATION WITH BALLOON ANGIOPLASTY IN PATIENTS WITH CORONARY ARTERY DISEASE

PATRICK W. SERRUYS, M.D., PETER DE JAEGERE, M.D., FERDINAND KIEMENEIJ, M.D., CARLOS MACAYA, M.D., WOLFGANG RUTSCH, M.D., GUY HEYNDRICKX, M.D., HÅKAN EMANUELSSON, M.D., JEAN MARCO, M.D., VICTOR LEGRAND, M.D., PIERRE MATERNE, M.D., JORGE BELARDI, M.D., ULRICH SIGWART, M.D., ANTONIO COLOMBO, M.D., JEAN JACQUES GOY, M.D., PAUL VAN DEN HEUVEL, M.D., JUAN DELCAN, M.D., AND MARIE-ANGÈLE MOREL, M.SC., FOR THE BENESTENT STUDY GROUP*

**Abstract** *Background.* Balloon-expandable coronary-artery stents were developed to prevent coronary restenosis after coronary angioplasty. These devices hold coronary vessels open at sites that have been dilated. However, it is unknown whether stenting improves long-term angiographic and clinical outcomes as compared with standard balloon angioplasty.

*Methods.* A total of 520 patients with stable angina and a single coronary-artery lesion were randomly assigned to either stent implantation (262 patients) or standard balloon angioplasty (258 patients). The primary clinical end points were death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for coronary-artery bypass surgery, or a second percutaneous intervention involving the previously treated lesion, either at the time of the initial procedure or during the subsequent seven months. The primary angiographic end point was the minimal luminal diameter at follow-up, as determined by quantitative coronary angiography.

*Results.* After exclusions, 52 patients in the stent group (20 percent) and 76 patients in the angioplasty group (30 percent) reached a primary clinical end point (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; $P = 0.02$). The difference in clinical-event rates was explained mainly by a reduced need for a second coronary angioplasty in the stent group (relative risk, 0.58; 95 percent confidence interval, 0.40 to 0.85; $P = 0.005$). The mean ($\pm$SD) minimal luminal diameters immediately after the procedure were $2.48\pm0.39$ mm in the stent group and $2.05\pm0.33$ mm in the angioplasty group; at follow-up, the diameters were $1.82\pm0.64$ mm in the stent group and $1.73\pm0.55$ mm in the angioplasty group ($P = 0.09$), which correspond to rates of restenosis (diameter of stenosis, $\geq$50 percent) of 22 and 32 percent, respectively ($P = 0.02$). Peripheral vascular complications necessitating surgery, blood transfusion, or both were more frequent after stenting than after balloon angioplasty (13.5 vs. 3.1 percent, $P<0.001$). The mean hospital stay was significantly longer in the stent group than in the angioplasty group (8.5 vs. 3.1 days, $P<0.001$).

*Conclusions.* Over seven months of follow-up, the clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty. However, this benefit was achieved at the cost of a significantly higher risk of vascular complications at the access site and a longer hospital stay. (N Engl J Med 1994;331:489-95.)

IMPLANTATION of an intracoronary stent in conjunction with balloon angioplasty is not only highly effective in treating acute vessel closure due to balloon-induced dissection, but it may also reduce the rate of restenosis.[1-4] Unfortunately, all stents currently available are metallic and thus thrombogenic, a problem that necessitates anticoagulation therapy.[5,6] This therapy exposes the patient to an increased risk of major bleeding and vascular complications, which may prolong the hospital stay.[7] Despite these drawbacks and although the superiority of stent implantation over standard balloon angioplasty has not yet been proved, stenting has been used increasingly. Therefore, we conducted a multicenter, randomized study comparing stent implantation and balloon angioplasty with respect to their safety and efficacy

From the University Hospital Rotterdam Dijkzigt, Thorax Center, Rotterdam, the Netherlands (P.W.S., P.J., M.A.M.); Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands (F.K.); University Hospital San Carlos, Madrid, Spain (C.M.); Universitätsklinikum Rudolf Virchow, Charlottenburg, Berlin, Germany (W.R.); Onze Lieve Vrouwe Kliniek, Aalst, Belgium (G.H.); Sahlgrenska Hospital, Goteborg, Sweden (H.E.); Clinique Pasteur, Toulouse, France (J.M.); Sart-Tilman Centre Hospitalier Universitaire, Liege, Belgium (V.L.); Hôpital de la Citadelle, Liege, Belgium (P.M.); Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (J.B.); Royal Brompton National Heart and Lung Institute, London (U.S.); Centro Cuore Columbus, Milan, Italy (A.C.); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (J.J.G.); Middelheim Ziekenhuis, Antwerp, Belgium (P.H.); and Gregorio Maranon, Madrid, Spain (J.D.). Address reprint requests to Dr. Serruys at the Catheterization Laboratory, Thorax Center, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands.

Supported in part by a grant from Johnson and Johnson Interventional Systems, Warren, N.J.; Schneider and Co., Bülach, Switzerland; and Lorex Pharmaceutica BV, Maarssen, the Netherlands.

*The remaining investigators in the Benestent Study Group are listed in the Appendix.

in patients with stable angina pectoris and a single new lesion in a coronary artery.

## METHODS

### Selection of Patients

Patients scheduled to undergo coronary angioplasty because of stable angina due to a single new lesion in a coronary artery were eligible for the study if they had no contraindication to anticoagulant or antiplatelet therapy and if they were also suitable candidates for coronary bypass surgery. The target lesion needed to be less than 15 mm long and to be located in a vessel more than 3 mm in diameter that supplied normally functioning myocardium. Patients with an ostial lesion, a lesion at a bifurcation, or a lesion in a previously grafted vessel were excluded from the study, as were patients in whom an intracoronary thrombus was suspected.

The study was carried out according to the principles of the Declaration of Helsinki. Oral or written informed consent according to local practice was obtained for every patient.

### Randomization

Patients were randomly assigned by telephone from a central office to either implantation of a Palmaz–Schatz stent or balloon angioplasty. To ensure an equal distribution of treatments in each center, we developed the randomization sequence on a site basis in blocks of six treatment assignments.

### Balloon Angioplasty and Stent Implantation

Balloon angioplasty and stent implantation were performed according to standard clinical practice by the femoral approach. The stent was deployed by inflating a balloon over which the collapsed stent was fitted. Inflation of the balloon expanded the stent. After the implantation of the stent, the stented area was often dilated further by standard balloon angioplasty. All patients received 250 to 500 mg of aspirin daily and 75 mg of dipyridamole three times a day; this treatment was started the day before the procedure and was continued for six months. During the procedure, patients receiving a stent were treated with a continuous infusion of dextran (1000 ml) and a bolus dose of 10,000 U of heparin, repeated if necessary, followed by a combination of heparin and oral anticoagulation therapy (with warfarin) after the removal of the sheath and titrated by measuring the prothrombin time and either the activated partial-thromboplastin time or the activated clotting time. The dose of heparin was decreased progressively after the prothrombin time had been in the therapeutic range (international normalized ratio, 2.5 to 3.5) for at least 36 hours. Warfarin therapy was continued for three months. The patients who underwent balloon angioplasty received only 10,000 U of heparin during that procedure, followed by an additional bolus dose or a continuous infusion if deemed necessary. In addition, both treatment groups received calcium antagonists until discharge from the hospital.

### Clinical and Angiographic Follow-up

Patients were seen in the outpatient clinic after one, three, and six months for an interview, physical examination, and electrocardiogram. Exercise testing was performed before the second cardiac catheterization and coronary angiography at six months. If a revascularization procedure involving the treated segment had been performed before the six-month angiography, the most recent angiogram obtained before this intervention, if available, was used as the follow-up angiogram, regardless of the timing of the second intervention. If the time to follow-up angiography was less than three months and no second intervention was performed, the patient was asked to undergo angiography again at six months. In the absence of a second angiogram at six months, the angiogram obtained most recently within the previous three months was used, if available, provided that no end point had occurred.

Three angiograms were obtained for each patient — one just before the intervention, one immediately after, and one at follow-up. All the angiograms were analyzed by the Cardiovascular Angiography Analysis System and sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands). To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier.[8]

### End Points

The primary clinical end points were whichever of the following occurred first: death, a cerebrovascular accident, myocardial infarction, bypass surgery, or a second percutaneous intervention involving the previously treated lesion between the time of the initial procedure and the angiography performed at 6 months (±4 weeks) (or at 7 months if no angiography was performed at 6 months). The indication for a second intervention or for bypass surgery had to be substantiated by symptoms or by electrocardiographic or scintigraphic evidence of myocardial ischemia at rest or during exercise. All events were reviewed by the critical-event committee, which was unaware of the treatment assignments.

Death was defined to include all deaths, regardless of cause. Cerebrovascular accidents occurring in patients receiving anticoagulant therapy were considered to be intracranial hemorrhages unless unequivocally demonstrated otherwise. Myocardial infarction was diagnosed if there were new pathologic Q waves according to the Minnesota Code[9] or if there was an increase in serum creatin kinase to more than twice the normal value, together with a pathologic increase in myocardial isoenzymes. Bypass surgery was defined to include emergency or elective bypass surgery involving th previously treated segment. Emergency bypass surgery was define as involving an immediate transfer from the angioplasty suite to th operating room during the initial phase of treatment. "Bailout stent implantation was defined as the placement of a stent in th event of Thrombolysis in Myocardial Infarction (TIMI) grade 0 c 1 flow after angioplasty or in the case of worsening of the base-lin TIMI flow by one grade.[10] In all instances, prolonged balloon an gioplasty had to be attempted before bailout stenting was consic ered. By design, stent implantation as a bailout procedure was con sidered equivalent to emergency bypass surgery but was remove retroactively from the analysis of primary end points, since it currently perceived as an integral part of an angioplasty strateg Only the untoward clinical events associated with such stentin were counted as end points. Second interventions were those invol ing a previously treated lesion that followed the initial procedur which was considered complete when the guiding catheter was r moved from the arterial sheath. Revascularization (surgical or pe cutaneous) involving other coronary arteries did not constitute end point.

The primary angiographic end point was the minimal lumin diameter at follow-up. For each treated segment, this value w calculated from the mean values obtained in multiple matched pr jections.

Secondary end points included (1) the angiographic success ra defined as the rate of achievement of less than 50 percent steno on visual assessment; (2) the procedural success rate, defined as t rate of achievement of less than 50 percent stenosis on quantitati assessment, without the occurrence of clinical events during t hospital stay; (3) the functional class according to the classific tion of the Canadian Cardiovascular Society at six months or at t time of intercurrent angiography and second intervention; (4) t results of exercise testing at six months or earlier, if clinically in cated; (5) the rate of restenosis (stenosis ≥50 percent at follow-u at six months.

### Power Calculations and Statistical Analysis

At the outset of the study, the size of the required sample (4 patients) was based on an assumed rate of clinical events of percent in the angioplasty group and a reduction of that rate by percent in the stent group (by a two-sided test with an alpha error 0.05 and a power of 0.80). To compensate for unsuccessful interv tions and losses to follow-up, the sample was enlarged by 10 perc (to 470 patients). In addition, to adjust for a loss of power due t planned interim analysis, the sample was increased by another percent, reaching a final size of 520 patients.[11]

The main clinical analysis consisted of a single comparison

A3712

CRDS01432015

tween the two study groups with respect to the primary clinical end point, regardless of its time of occurrence; this analysis involved all randomized patients with the exceptions of three patients found after randomization not to be eligible and of one patient who withdrew informed consent for further treatment and follow-up according to the intention-to-treat principle. The clinical events were ranked according to the highest category of severity on the following scale: death, cerebrovascular accident, myocardial infarction, emergency bypass surgery, elective bypass surgery, and repeat percutaneous intervention.

The main angiographic analysis consisted of a single comparison between the two study groups with respect to minimal luminal diameter and was performed according to the intention-to-treat principle.

Continuous variables are expressed as means ±SD and were compared by the unpaired Student's t-test. The chi-square test with Yates' correction was used to compare proportions. Discrete variables are expressed as counts and percentages and are compared in terms of relative risks (for stenting as compared with angioplasty), with 95 percent confidence intervals calculated by the formula of Greenland and Robins.[12] All statistical tests were two-tailed.

## Results

### Characteristics of the Patients

Between June 1991 and March 1993, 520 patients were randomly assigned to stent implantation (262 patients) or balloon angioplasty (258 patients) at 28 participating centers. Of these 520 patients, 4 were excluded from further analysis, 3 in the stent group and 1 in the angioplasty group. One patient withdrew his informed consent and left the hospital without receiving treatment, two other patients did not undergo coronary revascularization because their lesions proved to be unimportant during on-line quantitative coronary angiography at the time of the intended intervention, and one patient participated in another study with an investigational drug. There were no differences in base-line characteristics between the two study groups (Tables 1 and 2).

### In-Hospital Clinical Outcomes

Of the remaining 259 patients randomly assigned to receive stents, 14 (5.4 percent) did not receive a stent but were treated successfully with balloon angioplasty. The reasons for this crossover were the withdrawal of informed consent in five, the physician's preference because of the patient's unfavorable anatomy (e.g., small vessel size) or angiographic evidence of thrombus in three, and failure to cross the lesion with the stent in six. In addition, stent implantation was unsuccessful in 10 patients: 6 because the lesion was not dilated beforehand and 4 because the stent could not be deployed. Of these 10 patients, 8 underwent bypass surgery that was urgent in 3 and elective in 5. The remaining two patients, who unexpectedly had totally occluded coronary arteries that could not be recanalized, were treated medically.

Of the 257 remaining patients randomly assigned to balloon angioplasty, 13 (5.1 percent) received stents for the following reasons: acute vessel closure in 1, flow-limiting dissection in 11, and a suboptimal angiographic result in 1. Of these 13 patients, 2 were referred for urgent bypass surgery and 1 had a non-Q-wave myocardial infarction. In addition, three other patients who had complicated balloon angioplasty and in whom no bailout stent implantation was attempted underwent urgent bypass surgery. Therefore, the angiographic success rate was 96.9 percent in the stent group and 98.1 percent in the angioplasty group, whereas the procedural success rates were 92.7 and 91.1 percent, respectively.

The ranking and the total number of clinical events occurring in the hospital are shown in Table 3. The composite rate for all in-hospital events was similar in both groups (16 events or 6.2 percent in the angioplasty group vs. 18 events or 6.9 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.58 to 2.14). There were no in-hospital deaths in either group; one patient treated with balloon angioplasty had an intracranial hemorrhage. There was no difference between groups in the incidence of Q-wave and non-Q-wave infarction (3.1 percent in the angioplasty group vs. 3.4 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.44 to 2.85) or in the need for urgent or elective cardiac surgery or second angioplasty during the hospital stay (2.7 percent in the angioplasty group vs. 3.5 percent in the stent group; relative risk, 1.28; 95 percent confidence interval, 0.48 to 3.37).

Angiographically documented stent thrombosis during the hospital stay occurred in 3.5 percent of patients, an incidence similar to that of subacute vessel closure after balloon angioplasty (2.7 percent). It is noteworthy that no stent thrombosis occurred in the 13 patients treated with a bailout stent. However, the incidence of bleeding and vascular complications was

Table 1. Base-Line Clinical Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis.*

| Characteristic | Angioplasty (N = 257) | Stent (N = 259) |
|---|---|---|
| Age (yr) | 58±10 | 57±9 |
| Weight (kg) | 79±13 | 78±11 |
| Height (cm) | 171±9 | 171±8 |
| | *no. (%)* | *no. (%)* |
| Male sex | 212 (82) | 207 (80) |
| Ever smoked | 124 (48) | 119 (46) |
| Current smoker | 60 (23) | 62 (24) |
| Diabetes mellitus | 16 (6) | 17 (7) |
| Previous conditions | | |
| Myocardial infarction | 48 (19) | 52 (20) |
| Coronary-artery bypass grafting | 5 (2) | 0 |
| Angioplasty | 8 (3) | 5 (2) |
| Hypertension | 89 (35) | 80 (31) |
| Hypercholesterolemia | 95 (37) | 89 (34) |
| Stroke | 6 (2) | 6 (2) |
| Peripheral vascular disease | 8 (3) | 10 (4) |
| Exertional angina (CCS class)† | | |
| I | 9 (4) | 9 (3) |
| II | 75 (29) | 82 (32) |
| III | 130 (51) | 125 (48) |
| IV | 20 (8) | 16 (6) |
| None | 23 (9) | 27 (10) |
| Mixed | 89 (35) | 89 (34) |

*Plus-minus values are means ±SD.

†According to the classification system of the Canadian Cardiovascular Society (CCS).

A3713

CRDS01432016

significantly higher after stent implantation than after balloon angioplasty (13.5 vs. 3.1 percent; relative risk, 4.34; 95 percent confidence interval, 2.05 to 9.18; P<0.001).

The mean hospital stay was 8.5 days in the stent group and 3.1 days in the angioplasty group (P<0.001).

### Clinical Outcomes at Seven Months

The numbers of various types of clinical events at seven months among all 516 patients are shown in Table 3. A primary clinical end point was reached by 76 of the 257 patients randomly assigned to balloon angioplasty (30 percent), as compared with 52 of the 259 patients randomly assigned to stent implantation (20 percent) (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). This difference in long-term clinical outcome is shown in the cumulative distribution curves for the primary clinical end point in both treatment groups (Fig. 1D). The favorable long-term outcome in the stent group was also partly reflected in the difference between the two groups in functional class at the time of the second angiography (Table 4). The most striking difference in clinical outcomes was the significantly reduced need for an elective second revascularization by means of percutaneous intervention involving the target lesion. There was a 42 percent reduction favoring stent implantation.

During the study, three patients died, one in the

Table 2. Angiographic Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis and Characteristics of the Procedures They Underwent.*

| Characteristic | Angioplasty (N = 257) | Stent (N = 259) |
|---|---|---|
| | *number (percent)* | |
| Artery dilated | | |
| Right coronary | 72 (28) | 60 (23) |
| Left anterior descending | 159 (62) | 165 (64) |
| Left circumflex | 26 (10) | 34 (13) |
| Type of lesion† | | |
| Concentric | 118 (46) | 130 (50) |
| Eccentric | | |
| IA | 33 (13) | 34 (13) |
| IB | 62 (24) | 57 (22) |
| IIA | 10 (4) | 10 (4) |
| IIB | 13 (5) | 10 (4) |
| Tandem | 0 | 1 (0.4) |
| Multiple irregularities | 21 (8) | 16 (6) |
| Occluded (TIMI 0 or 1)‡ | 5 (2) | 9 (3) |
| Calcified | 27 (11) | 29 (11) |
| Length (mm) | 6.96±2.57 | 7.06±2.56 |
| Thrombus after procedure§ | 10 (4) | 3 (1) |
| Dissection¶ | | |
| No | 145 (56) | 215 (83) |
| Type A | 43 (17) | 21 (8) |
| Type B | 57 (22) | 16 (6) |
| Type C | 9 (4) | 5 (2) |
| Type E | 1 (0.4) | 1 (0.4) |
| Type F | 2 (0.8) | 0 |
| Nominal size, stent or balloon (mm) | 3.29±0.38 | 3.31±0.34 |
| Balloon/stent artery ratio | 1.12±0.15 | 1.12±0.15 |
| Largest balloon size (mm)‖ | 3.30±0.38 | 3.40±0.40 |
| Maximal pressure (atmospheres) | 9±3 | 10±8 |
| Total inflation time (sec) | 399±359 | 180±178 |

*The interobserver and intraobserver variability of these morphologic measures has previously been reported by the core laboratory.[13] Plus-minus values are means ±SD.

†According to the classification system of Ambrose et al.[14]

‡According to the TIMI Study Group.[10]

§According to the definition of Ellis et al.[15]

¶According to the classification system of Dorros et al.[16]

‖Nominal size.

Table 3. Frequency of Primary Clinical End Points in the Hospital and at Seven Months in Descending Order of Severity, Total Number of Events, and Quantitative Comparison of Immediate and Long-Term Angiographic Results.*

| Event | Angioplasty (N = 257) | Stent (N = 259) | Relative Risk (95% CI) |
|---|---|---|---|
| | *number (percent)* | | |
| Death | | | |
| In hospital | 0 | 0 | — |
| At 7 mo | 1 (0.4) | 2 (0.8) | 1.98 (0.18–21.75) |
| All events | 1 (0.4) | 2 (0.8) | 1.98 (0.18–21.75) |
| Cerebrovascular accident | | | |
| In hospital | 1 (0.4) | 0 | — |
| At 7 mo | 2 (0.8) | 0 | — |
| All events | 2 (0.8) | 0 | — |
| Q-wave MI | | | |
| In hospital | 2 (0.8) | 5 (1.9) | 2.48 (0.49–12.67) |
| At 7 mo | 4 (1.6) | 7 (2.7) | 1.74 (0.51–5.86) |
| All events | 5 (1.9) | 7 (2.7) | 1.39 (0.45–4.32) |
| Non–Q-wave MI | | | |
| In hospital | 6 (2.3) | 4 (1.5) | 0.66 (0.19–2.32) |
| At 7 mo | 6 (2.3) | 4 (1.5) | 0.66 (0.19–2.32) |
| All events | 7 (2.7) | 4 (1.5) | 0.57 (0.17–1.91) |
| Urgent CABG | | | |
| In hospital | 4 (1.6) | 5 (1.9) | 1.24 (0.34–4.57) |
| At 7 mo | 4 (1.6) | 5 (1.9) | 1.24 (0.34–4.57) |
| All events | 5 (1.9) | 6 (2.3) | 1.19 (0.37–3.85) |
| Elective CABG | | | |
| In hospital | 0 | 3 (1.2) | — |
| At 7 mo | 6 (2.3) | 8 (3.1) | 1.32 (0.47–3.76) |
| All events | 6 (2.3) | 10 (3.9) | 1.65 (0.61–4.48) |
| Repeat PTCA | | | |
| In hospital | 3 (1.2) | 1 (0.4) | 0.33 (0.03–3.16) |
| At 7 mo | 53 (20.6) | 26 (10.0) | 0.49 (0.32–0.75) |
| All events | 60 (23.3) | 35 (13.5) | 0.58 (0.40–0.85) |
| Any event | | | |
| In hospital | 16 (6.2) | 18 (6.9) | 1.12 (0.58–2.14) |
| At 7 mo | 76 (29.6) | 52 (20.1) | 0.68 (0.50–0.92) |

| Variable† | Angioplasty (N = 240) | Stent (N = 237) | P Value |
|---|---|---|---|
| | *mean ±SD* | | |
| Reference diameter (mm) | | | |
| Before | 3.01±0.46 | 2.99±0.45 | NS |
| After | 3.09±0.44 | 3.16±0.43 | 0.045 |
| Follow-up | 3.05±0.49 | 2.96±0.48 | 0.04 |
| Minimal luminal diameter (mm) | | | |
| Before | 1.08±0.31 | 1.07±0.33 | NS |
| After | 2.05±0.33 | 2.48±0.39 | <0.001 |
| Follow-up | 1.73±0.55 | 1.82±0.64 | 0.09‡ |
| Stenosis (%) | | | |
| Before | 64±10 | 64±10 | NS |
| After | 33±8 | 22±8 | <0.001 |
| Follow-up | 43±16 | 38±18 | 0.003 |
| Restenosis rate (%) | 32 | 22 | 0.02 |
| Gain (mm) | 0.97±0.39 | 1.40±0.44 | <0.001 |
| Loss (mm) | 0.32±0.47 | 0.65±0.57 | <0.001 |
| Net gain (mm) | 0.65±0.59 | 0.75±0.66 | 0.09 |

*"All events" refers to the total count of events at seven months (i.e., if a patient required repeat angioplasty and later coronary-artery bypass grafting, the total count at seven months would reflect both events, not just the first that occurred). CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and NS not significant.

†Reference values are the interpolated diameters of normal vessels; gain, the minimal luminal diameter after the procedure minus the value obtained before the procedure; loss, the minimal luminal diameter after the procedure minus the follow-up value; and net gain, the minimal luminal diameter at follow-up minus the value obtained before the procedure.

‡P = 0.08 and P = 0.03 for the difference in minimal luminal diameter between the two study groups at follow-up when the pre-intervention lumen and vessel size, respectively, were used as covariates.

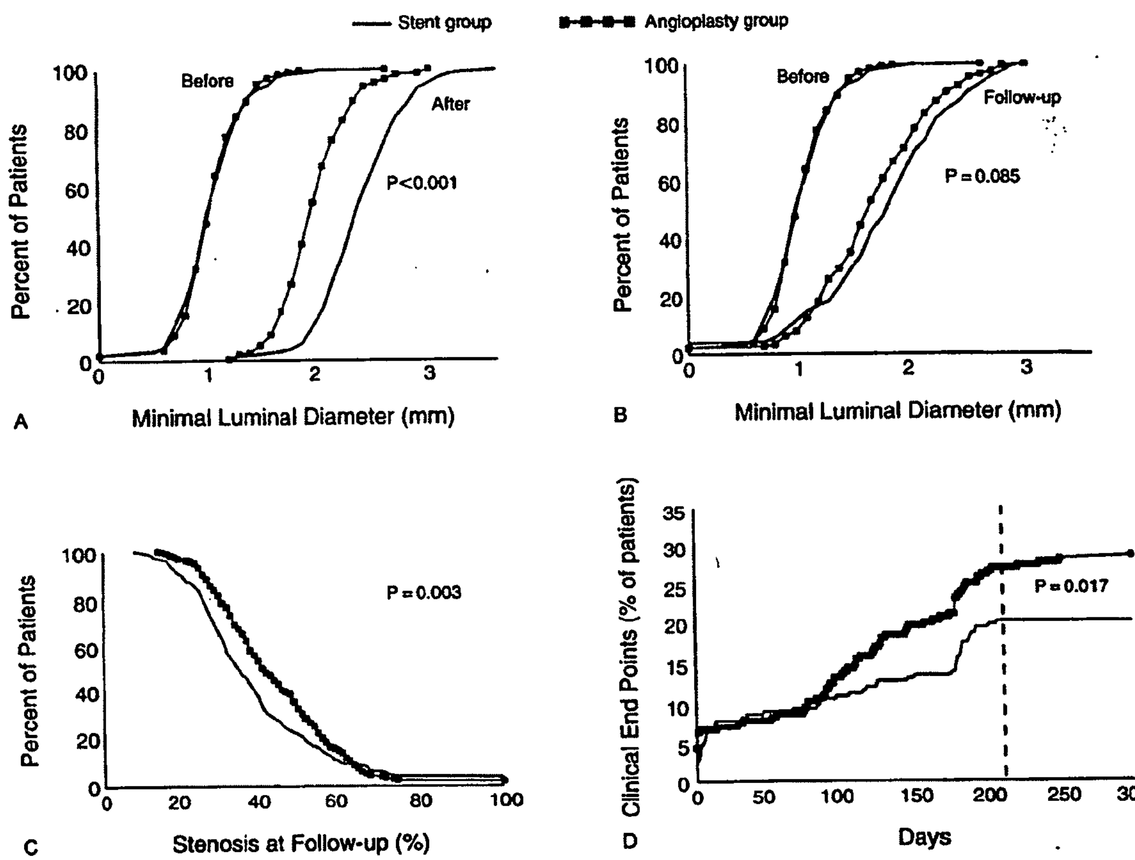



**Figure 1. Cumulative Frequency Distribution Curves for the Two Study Groups, Showing Minimal Luminal Diameters Measured before and after Intervention and at Follow-up, the Percentage of Stenosis at Follow-up, and the Percentage of Patients with Clinical End Points.**

Significant differences were apparent that consistently favored the stent group over the angioplasty group with respect to the increased minimal luminal diameter at intervention (Panel A) and follow-up (Panel B), the percentage of stenosis at follow-up (Panel C), and the incidence of major clinical events (Panel D). The vertical dashed line in Panel D indicates the end of the study.

angioplasty group and two in the stent group. One patient treated with balloon angioplasty committed suicide four months after the intervention. Two other patients died two and three weeks after successful stent implantations. In the first of these patients, death was preceded by chest pain associated with ST-segment elevation and was therefore thought to be related to a subacute occlusion. In the second patient, the cause of death was hypovolemic shock during surgical repair of an arteriovenous fistula. Although the stent was patent at the time of the pathological examination, the death was considered to be related to the stent.

### Angiographic Analysis

Angiographic follow-up data were obtained for 93 percent of the eligible patients (Table 3). The minimal luminal diameter at follow-up was greater after stent implantation than after balloon angioplasty ($1.82\pm0.64$ vs. $1.73\pm0.55$ mm, $P = 0.09$; median difference, 0.17 mm). The cumulative distribution of the minimal luminal diameter and percentage of stenosis are shown in Figure 1A, B, and C. The incidence of restenosis (the criterion for which was ≥50 percent stenosis) was 22 percent after stent implantation as compared with 32 percent after balloon angioplasty ($P = 0.02$).

## Discussion

We found that implantation of coronary stents in patients with stable angina and a single new coronary-artery lesion was associated with a rate of immediate clinical success similar to that of standard balloon angioplasty, but a significantly lower rate of restenosis. This translated into a superior long-term clinical outcome, mainly due to a reduced need for additional percutaneous intervention, at least according to the composite analysis of clinical end points. The advantage of this combined clinical end point is that it leads to a simple estimate of the effect of treatment. However, this analysis ignores the relative effect of various events (i.e., it considers death, a cerebrovascular accident, myocardial infarction, and the like to be equally harmful to the patient) and does not reflect the multiplicity of events that may occur (e.g., in a patient undergoing second angioplasty and surgery and ulti-

Table 4. Functional Class at Seven Months of Follow-up or at the Time of the Intercurrent Intervention for the 516 Patients Included in the Intention-to-Treat Analysis.*

| FUNCTIONAL CLASS† | ANGIOPLASTY (N = 257) | STENT (N = 259) |
|---|---|---|
| | *number (percent)* | |
| 0 (Asymptomatic) | 170 (66) | 190 (73) |
| 1–4 | 83 (32) | 67 (26) |
| 1 | 10 (4) | 12 (5) |
| 2 | 32 (12) | 28 (11) |
| 3 | 28 (11) | 15 (6) |
| 4 | 13 (5) | 12 (5) |
| Unknown | 4 (2) | 2 (0.8) |

*P = 0.07 for the comparison of functional classes according to treatment group (angioplasty vs. stent).

†The classes shown are those established by the Canadian Cardiovascular Society.

mately dying). To address this shortcoming, a count of all events is included in Table 3.

One of the major drawbacks of studies on the prevention of coronary restenosis is that at follow-up the angiographic knowledge of coronary anatomy may influence the physician's therapeutic decision and artificially increase the number of second interventions. This is especially true when the investigator is not kept unaware of the treatment assignments, as when a new device is tested. To circumvent this possible source of bias, a second intervention was considered an end point in this study only when it was substantiated on the basis of anginal symptoms or objective evidence of ischemia (Table 5). Only two second interventions in the angioplasty group and one in the stent group might not have been justified. Moreover, the fact that the cumulative curves for the composite clinical end points (Fig. 1D) diverged between day 75 and day 150 indicates that the difference in clinical outcome was not artificially driven by the angiographic findings at the time of the second catheterization.

Not unexpectedly, the incidence of major bleeding complications was significantly higher in the stent group (13.5 percent) than in the angioplasty group (3.1 percent). The overall incidence reported in the literature, expressed as a weighted average of groin hematomas and pseudoaneurysms, was 7.5 percent (range, 2.7 to 26 percent) and 4.2 percent (range, 0 to 10.8 percent), respectively.[17]

Table 5. Presence of Clinical Symptoms, Ischemic Signs, and Degree of Stenosis in Patients Who Underwent a Second Intervention at Follow-up.

| VARIABLE* | ANGIOPLASTY (N = 257) | STENT (N = 259) |
|---|---|---|
| No. of patients | 59 | 34† |
| No. with angina | 54 | 31 |
| No. with ECG changes at rest or during exercise | 14 | 8 |
| No. with neither angina nor ECG changes | 2 | 1 |
| No. with ETT performed | 24 | 14 |
| Percent stenosis — mean ±SD | 59±14 | 66±21‡ |

*ECG denotes electrocardiographic, and ETT exercise-tolerance test.

†The relative risk as compared with the angioplasty group was 0.57 (95 percent confidence interval, 0.39 to 0.84; P = 0.005).

‡P = 0.06 for the comparison of groups by unpaired Student's t-test.

Another significant difference between the two treatment groups was in the duration of hospitalization. However, Cohen et al. recently showed that length of stay, consumption of resources, and total costs were still substantially greater for bypass surgery than for stenting and that the initially higher in-hospital costs of stent implantation as compared with balloon angioplasty are compensated for by the reduction in subsequent interventions during follow-up.[18,19] The practitioner and the patient must, however, weigh a long hospital stay and a 13.5 percent risk of bleeding and vascular complications against the potential benefit of a reduction in the likelihood of clinical events from 30 percent to 20 percent.

It may be argued that the difference in drug therapy between the two study groups accounts for the observed differences in angiographic outcome and rate of restenosis. However, a number of clinical studies collectively rule out any beneficial effect of anticoagulant therapy on restenosis in humans.[20-25] Moreover, the degree of angiographically documented luminal loss was significantly higher after stent implantation than after balloon angioplasty (Table 3). Therefore, the beneficial angiographic and clinical effects of stent implantation are explained by the propensity of the stent to achieve a consistently greater increase in luminal diameter immediately after the procedure than is the case with balloon angioplasty, which is inherently limited by the well-described phenomenon of elastic recoil.[3,26]

It should be emphasized that in interpreting the favorable results observed in this trial, the restrictive nature of the criteria for inclusion and exclusion must be kept in mind, and thus the results may not be generalizable to other patients, indications, and types of stents. Finally, bleeding and vascular complications and the prolonged hospitalization remain major drawbacks of stent implantation and continue to hamper its acceptance in clinical practice.

## APPENDIX

The following institutions and investigators participated in the Benestent study. The number of patients enrolled at each center is given in parentheses.

University Hospital San Carlos, Madrid, Spain (76): F. Alfonso, J. Goicolea, R. Hernandez, and A. Iniguez; University Hospital Rotterdam Dijkzigt, Thorax Center, Rotterdam, the Netherlands (57): P.J. de Feyter and M. van den Brand; Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands (50): G.J. Laarman and R. vander Wieken; Universitätsklinikum Rudolf Virchow, Charlottenburg, Berlin, Germany (39): W. Rutsch; Onze Lieve Vrouwe Ziekenhuis, Aalst, Belgium (38): B. de Bruyne; Sahlgrenska Hospital, Goteborg, Sweden (36): P. Albertsson; Clinique Pasteur, Toulouse, France (32): J. Fajadet, S. Doucet, and O. Bar; Sart-Tilman Centre Hospitalier Universitaire, Liege, Belgium (32): V. Legrand; Hôpital de la Citadelle, Liege, Belgium (19): J. Boland; Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (19): J. Berrocal and R. Piraino; Royal Brompton National Heart and Lung Institute, London (12): N. Buller and K. Priestley; Centro

Cuore Columbus, Milan, Italy (11): L. Maiello; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (11): E. Eeckhout; Middelheim Ziekenhuis, Antwerp, Belgium (10): F. van den Brande; Gregorio Maranon, Madrid, Spain (10): E. Garcia; Ziekenhuis de Weezenlanden, Zwolle, the Netherlands (8): H. Suryapranata and J. Hoorntje; St. Antonius Ziekenhuis, Nieuwegein, the Netherlands (8): T. Plokker and G. Mast; Hospital Maggiore, Trieste, Italy (8): S. Klugmann, E. Della Grazia, and A. Salvi; Hôpital Cantonal Universitaire, Geneva, Switzerland (7): P. Urban and E. Camenzind; Academisch Ziekenhuis Groningen, Groningen, the Netherlands (6): P. den Heijer and R. van Dijk; Academic Medical Center, Amsterdam, the Netherlands (6): J. Piek and K. Koch; Christian Albrechts University, Kiel, Germany (6): R. Simon and G. Herrmann; Centre Cardiologique du Nord, Paris (5): M.C. Morice and T. Royer; St. James Hospital, Dublin, Ireland (5): P. Crean; Catharina Ziekenhuis, Eindhoven, the Netherlands (3): H. Bonnier, J. Koolen, and F. Bracke; Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels, Belgium (2): W. Wijns; Centre Hospitalier Régional et Universitaire, Nancy, France (2): N. Danchin and Y. Juillière; and the Polyclinique Volney, Rennes, France (2): C. Bourdonnec.

Ethics and Safety Committee: F. Verheugt, Free University Amsterdam, Amsterdam, the Netherlands; J. Tijssen, Academic Medical Center, Amsterdam, the Netherlands; and G. de Backer, State University Ghent, Ghent, Belgium.

Steering Committee: P.W. Serruys (chairman), H. Emanuelsson, G.R. Heyndrickx, P.P.T. de Jaegere, F. Kiemeneij (co-chairman), C. Macaya, J. Marco, and P. Materne.

Critical Event Committee: F. Kiemeneij (chairman), P.W. Serruys, P.P.T. de Jaegere, P.J. de Feyter, and P. van den Heuvel.

Angiographic Assessment Committee: P.P.T. de Jaegere (chairman), P.W. Serruys, W. Rutsch, B. de Bruyne, and V. Legrand.

Exercise Testing Committee: V. Legrand (chairman), G. Laarman, and N. Danchin.

Data Coordinating and Analysis Center and Quantitative Angiographic Core Laboratory: Cardialysis, Rotterdam, the Netherlands: M. Morel, A.G. Azar, G.A. van Es, J.P. Herrman, R. Melkert, J. Pameyer, and L.M. Rodenburg.

## References


1. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701-6.
2. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916-27.
3. de Jaegere PPT, Hermans WR, Rensing BJ, Strauss BH, de Feyter PJ, Serruys PW. Matching based on quantitative coronary angioplasty as a surrogate for randomized studies: comparison between stent implantation and balloon angioplasty of native coronary artery lesions. Am Heart J 1993;125:310-9.
4. Fischman DL, Savage MP, Ellis SG, et al. Restenosis after Palmaz-Schatz stent implantation. In: Serruys PW, Strauss BH, King SB III, eds. Restenosis after intervention with new mechanical devices. Vol. 131 of Developments in cardiovascular medicine. Dordrecht, the Netherlands: Kluwer Academic, 1992:191-205.
5. Schatz RA, Baim DS, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent: initial results of a multicenter study. Circulation 1991;83:148-61.
6. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991;324:13-7.
7. de Jaegere PPT, de Feyter PJ, van der Giessen WJ, Serruys PW. Endovascular stents: preliminary clinical results and future developments. Clin Cardiol 1993;16:369-78.
8. Serruys PW, Foley DP, de Feyter PJ, eds. Quantitative coronary angiography in clinical practice. Dordrecht, the Netherlands: Kluwer Academic, 1994.
9. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies: a classification system. Circulation 1960;21:1160-75.
10. The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: Phase I findings. N Engl J Med 1985;312:932-6.
11. Pocock SJ. Interim analyses for randomized clinical trials: the group sequential approach. Biometrics 1982;38:153-62.
12. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41:55-68.
13. Hermans WRM, Rensing BJ, Foley DP, et al. Therapeutic dissection after successful coronary balloon angioplasty: no influence on restenosis or on clinical outcome in 693 patients. J Am Coll Cardiol 1992;20:767-80.
14. Ambrose JA, Winters SL, Stern A, et al. Angiographic morphology and the pathogenesis of unstable angina pectoris. J Am Coll Cardiol 1985;5:609-16.
15. Ellis SG, Roubin GS, King SB III, Douglas JS Jr, Cox WR. Importance of stenosis morphology in the estimation of restenosis risk after elective percutaneous transluminal coronary angioplasty. Am J Cardiol 1989;63:30-4.
16. Dorros G, Cowley MJ, Simpson J, et al. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. Circulation 1983;67:723-30.
17. de Jaegere P, de Feyter P, Serruys PW. Intracoronary stenting. Curr Rev Interv Cardiol 1993;8:1-17.
18. Cohen DJ, Breall JA, Ho KK, et al. Economics of elective coronary revascularization: comparison of costs and charges for conventional angioplasty, directional atherectomy, stenting and bypass surgery. J Am Coll Cardiol 1993;22:1052-9.
19. Cohen DJ, Breall JA, Ho KK, et al. Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease: use of a decision-analytic model. Circulation 1994;89:1859-74.
20. Hirshfeld JW, Schwartz SS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. J Am Coll Cardiol 1991;18:647-56.
21. Ellis SG, Roubin GS, Wilentz J, Douglas JS Jr, King SB III. Effect of 18- to 24-hour heparin administration for prevention of restenosis after uncomplicated coronary angioplasty. Am Heart J 1989;117:777-82.
22. Perin EC, Turner SA, Ferguson JJ. Relationship between the response to heparin and restenosis following PTCA. Circulation 1990;82:Suppl III:III-497. abstract.
23. Faxon D, Spiro T, Minor S, et al. Enoxaparin, a low molecular weight heparin, in the prevention of restenosis after angioplasty: result of a double blind randomized trial. J Am Coll Cardiol 1992;19:Suppl A:258A. abstract.
24. Thornton MA, Gruentzig AR, Hollman J, King SB III, Douglas JS. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. Circulation 1984;69:721-7.
25. Urban P, Buller N, Fox K, Shapiro L, Bayliss J, Rickards A. Lack of effect of warfarin on the restenosis rate or on clinical outcome after balloon coronary angioplasty. Br Heart J 1988;60:485-8.
26. Rensing BJ, Hermans WR, Beatt KJ, et al. Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. Am J Cardiol 1990;66:1039-44.

# A3718-3878

# REDACTED

Guidant Press Releases > 2003

# Jan 2, 2003
# Guidant Reports Preliminary Results of DELIVER Clinical Trial

Conditions to Closing Guidant-Cook Merger Not Satisfied Company to Host Webcast/Conference Call January 3 at 8:30 AM EST

Indianapolis, Ind. - Guidant Corporation (NYSE and PCX: GDT), a world leader in the treatment of cardiac and vascular disease, today reported preliminary results of the DELIVER clinical trial. The DELIVER clinical trial was a randomized U.S. clinical study comparing the paclitaxel-coated ACHIEVE(tm) Drug Eluting Coronary Stent System, manufactured by Cook Incorporated, to the MULTI-LINK PENTA(tm) Coronary Stent System, manufactured by Guidant. The study was designed to demonstrate a 40 percent reduction in the primary endpoint of 270-day target vessel failure (TVF) for the ACHIEVE Drug Eluting Coronary Stent System, as compared to the PENTA Coronary Stent System.

While the final analysis of the DELIVER clinical results is still in progress, the preliminary analysis indicates that although there is a trend toward improvement in TVF, the primary endpoint will not be met. Additionally, while there appears to be a trend toward a reduced angiographic binary restenosis rate (ABRR), the planned 50 percent reduction in angiographic binary restenosis also will not be achieved. The percent reduction in both TVF and ABRR is less than expected due to the combination of excellent results in the PENTA Coronary Stent System control arm (9-month TVF of 14-15 percent and in-segment ABRR of 21-22 percent) and a higher-than-expected 11-12 percent TVF and 16-17 percent in-segment ABRR in the ACHIEVE arm of the study.

Based on these results, the conditions outlined in the previously announced Guidant-Cook Group Incorporated merger agreement are not expected to be satisfied. The terms of the merger agreement include a break-up fee of $50 million and an amendment to an existing stent delivery system agreement.

"Guidant"s collaboration with Cook represented a unique opportunity for both companies to advance drug eluting stent technologies in the field of vascular intervention," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant. "While the DELIVER study did not meet its primary endpoint, the results demonstrate the safety and a trend toward efficacy of the ACHIEVE Drug Eluting Coronary Stent System. In addition, the study further demonstrates the excellent clinical performance of the PENTA Coronary Stent System. We look forward to a continued business relationship with Cook as we work toward our mutual goal of advancing medical technology."
Guidant"s Everolimus Program on Schedule

Guidant continues to make significant progress in its internal everolimus program. "We are enthusiastic about our work with everolimus, which is on track with excellent pre-clinical results. We look forward to the first human implant of an everolimus eluting stent later this quarter under the Vision-E trial, a feasibility study for an everolimus eluting MULTI-LINK VISION(tm) Coronary Stent System utilizing our proprietary TRUE COAT(tm) polymer," continued Capek. "In addition, our agreement in principle announced today to acquire the assets of Biosensors" everolimus eluting stent program strengthens our internal everolimus efforts."

Guidant issued a press release today announcing an agreement in principle to acquire certain assets of Biosensors International"s everolimus eluting stent program. The agreement is expected to provide Guidant with an exclusive worldwide license to Biosensors" intellectual property in the field of everolimus eluting stents, and a nonexclusive license to Biosensors" drug and bioabsorbable p

EXHIBIT
tabbies
PX 113

formulation technology for use with other drugs.
Webcast

Guidant will host a live webcast briefing tomorrow, January 3, at 8:30 AM EST to discuss these events and 2003 financial guidance. Guidant President and CEO Ronald W. Dollens and John M. Capek, Ph.D., president, Vascular Intervention, will host the briefing. The webcast will be accessible through Guidant"s website at www.guidant.com/webcast or at CCBN's individual investor center at www.companyboardroom.com. The webcast will be archived on both websites for future on-demand replay.

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to millions of cardiac and vascular patients worldwide. The company, driven by a strong entrepreneurial culture of more than 10,000 employees, develops, manufactures and markets a broad array of products and services that enable less-invasive care for some of life"s most threatening medical conditions. For more information visit www.guidant.com.

NOTE TO MEDIA: For more information about Guidant, including its products and services, please visit the company"s newsroom at www.guidant.com/newsroom.

This release includes forward-looking statements concerning anticipated clinical results, the company"s relationship with Cook, and the company"s everolimus program. The statements are based on assumptions about many important factors, including final adjudication of clinical results, litigation, product development timelines, the closing of the Biosensors transaction (which remains subject, among other things, to further due diligence and completion of a definitive agreement), and other factors identified on Exhibit 99.1 to the company"s most recent 10-Q. Actual results may differ materially. The company does not undertake to update its forward-looking statements.

System requirements for the webcast include Internet Explorer 5.0 (or higher) or Netscape Navigator 4.0 (or higher). Users also should have the most recent version of Windows Media Player, which can be downloaded for free at http://www.microsoft.com/windows/windowsmedia/en/download/. Users may experience varying levels of performance based on their connection speed, system capabilities and presence of a corporate firewall. To ensure a connection, users should go to the program five to 15 minutes before its start.

Guidant Press Releases > 2002

**Mar 7, 2002**

## Guidant Halts Further Development on Actinomycin-D Drug Eluting Stent Program

Company to Host Webcast/Conference Call Today

**Indianapolis, IN** - Guidant Corporation (NYSE and PCX: GDT), a global leader in cardiac and vascular technology, today reported preliminary results of its international ACTION clinical trial evaluating a drug eluting stent system utilizing actinomycin-D.

Preliminary results of the study indicate that actinomycin-D is not effective in preventing restenosis and patients treated with actinomycin-D eluting stents have an unacceptably high target lesion revascularization rate.

Guidant observed this data during the process of monitoring the clinical follow-up of the first 90 patients enrolled in the study. As a result, Guidant's actinomycin-D drug eluting stent program has been halted. The company will not go forward with an IDE submission for the U.S. pivotal trial using this compound.

"Guidant's overriding interest is in the well-being of the patients involved in the study," said John M. Capek, Ph.D., president, Vascular Intervention, Guidant Corporation. "We are working closely with the clinicians involved in the study to ensure appropriate follow-up for the patients.

"Despite these results for the actinomycin-D program, we continue to see great promise for drug eluting stents, and we believe that the processes, capabilities and strategic direction of Guidant's drug eluting stent program are solid," Capek continued. "We will continue to focus on the more advanced paclitaxel program with Cook Incorporated, which recently completed enrollment of 1,042 patients in DELIVER, and we will pursue the development of other drug eluting stents utilizing Guidant's proprietary elution technology and market-leading stent designs."

### Conference Call/Webcast

Guidant will conduct a live webcast today, Thursday, March 7, at 8:30 a.m. EST. The live webcast of Guidant's conference call will be accessible through Guidant's website at www.guidant.com/webcast or at CCBN's individual investor center at www.companyboardroom.com. The webcast will be archived on both websites for future on-demand replay.

The call will be hosted by Guidant's President and CEO Ronald W. Dollens and will feature a review of Guidant's drug eluting stent program. Also participating on the call will be John M. Capek, Ph.D. and Thomas J. Linnemeier, M.D., Senior Vice President and Chief Medical Officer, Guidant Vascular Intervention.

EXHIBIT
tabbies
PX 112

Guidant Corporation pioneers lifesaving technology, giving an opportunity for better life today to 7 million cardiac and vascular patients worldwide. The company, driven by a strong entrepreneurial culture of 10,000 employees, develops, manufactures and markets a broad array of products and services that enable less invasive care for some of life's most threatening medical conditions.

This release includes forward-looking statements concerning drug-eluting stents and our progress with them. The forward-looking statements are based on assumptions about

many important factors, including new product development, regulatory approvals, litigation and other factors listed on exhibit 99 to the company's most recent 10-Q. As such, they involve risks and uncertainties that could cause actual results to differ materially. The company does not undertake to update its forward-looking statements.

Email Page Print

US006746773B2

(12) **United States Patent**
**Llanos et al.**

(10) **Patent No.: US 6,746,773 B2**
(45) **Date of Patent: Jun. 8, 2004**

(54) **COATINGS FOR MEDICAL DEVICES**

(75) Inventors: **Gerard H. Llanos**, Stewartsville, NJ (US); **Pallassana Narayanan**, Belle Mead, NJ (US); **Mark B. Roller**, North Brunswick, NJ (US); **Angelo Scopelianos**, Whitehouse Station, NJ (US)

(73) Assignee: **Ethicon, Inc.**, Somerville, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/962,292**

(22) Filed: **Sep. 25, 2001**

(65) **Prior Publication Data**

US 2002/0094440 A1 Jul. 18, 2002

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/675,882, filed on Sep. 29, 2000, now abandoned.

(51) **Int. Cl.**[7] ............................................... **B23B 27/00**

(52) **U.S. Cl.** ................ **428/421**; 604/890.1; 604/891.1; 604/265; 623/1.42; 623/1.43; 623/1.44; 623/1.49

(58) **Field of Search** .......................... 604/891.1, 890.1, 604/265; 623/1.42, 1.44, 1.43, 1.49; 523/105, 112, 113; 525/937; 524/546; 428/421, 422

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | | | |
|---|---|---|---|---|---|
| 3,051,677 | A | | 8/1962 | Rexford | |
| 3,779,805 | A | | 12/1973 | Alsberg | |
| 4,413,359 | A | * | 11/1983 | Akiyama et al. | 3/1 |
| 4,423,183 | A | * | 12/1983 | Close | 524/546 |
| 4,733,665 | A | | 3/1988 | Palmaz | |
| 4,749,585 | A | | 6/1988 | Greco et al. | |
| 4,800,882 | A | | 1/1989 | Gianturco | |
| 4,871,357 | A | | 10/1989 | Hsu et al. | |
| 4,876,109 | A | | 10/1989 | Mayer et al. | |
| 4,886,062 | A | | 12/1989 | Wiktor | |
| 5,047,020 | A | | 9/1991 | Hsu | |
| 5,053,048 | A | | 10/1991 | Pinchuk | |
| 5,176,972 | A | * | 1/1993 | Bloom et al. | 430/14 |
| 5,185,408 | A | | 2/1993 | Tang et al. | |
| 5,336,518 | A | | 8/1994 | Narayanan et al. | |
| 5,342,348 | A | | 8/1994 | Kaplan | |
| 5,368,566 | A | | 11/1994 | Crocker | |
| 5,380,299 | A | | 1/1995 | Fearnot et al. | |
| 5,383,853 | A | | 1/1995 | Jung et al. | |
| 5,383,928 | A | | 1/1995 | Scott et al. | |
| 5,403,341 | A | | 4/1995 | Solar | |
| 5,417,969 | A | | 5/1995 | Hsu et al. | |
| 5,443,458 | A | | 8/1995 | Eury | |
| 5,447,724 | A | | 9/1995 | Helmus et al. | |
| 5,464,650 | A | | 11/1995 | Berg et al. | |
| 5,545,208 | A | | 8/1996 | Wolff et al. | |
| 5,569,463 | A | | 10/1996 | Helmus et al. | |
| 5,575,818 | A | | 11/1996 | Pinchuk | |
| 5,591,224 | A | | 1/1997 | Schwartz et al. | |
| 5,604,283 | A | * | 2/1997 | Wada et al. | 524/236 |
| 5,616,608 | A | | 4/1997 | Kinsella et al. | |
| 5,632,771 | A | | 5/1997 | Boatman et al. | |
| 5,632,776 | A | | 5/1997 | Kurumatani et al. | |
| 5,632,840 | A | | 5/1997 | Campbell | |
| 5,635,201 | A | | 6/1997 | Fabo | |
| 5,665,728 | A | | 9/1997 | Morris et al. | |
| 5,679,400 | A | | 10/1997 | Tuch | |
| 5,684,061 | A | * | 11/1997 | Ohnishi et al. | 523/114 |
| 5,691,311 | A | | 11/1997 | Maraganore et al. | |
| 5,697,967 | A | | 12/1997 | Dinh et al. | |
| 5,713,949 | A | | 2/1998 | Jayaraman | |
| 5,716,981 | A | | 2/1998 | Hunter et al. | |

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| DE | 19723723 A | 12/1998 |
| EP | 0 568 310 A1 | 4/1993 |
| EP | 0633032 A | 1/1995 |
| EP | 747069 | 12/1996 |
| EP | 0 815 803 A | 1/1998 |
| EP | 0 950 386 A2 | 4/1999 |
| EP | 0 968 688 A | 1/2000 |
| EP | 1 192 957 A | 4/2002 |
| WO | WO 98/36784 A1 | 2/1998 |
| WO | WO 9808463 A | 3/1998 |
| WO | WO 00/27455 A1 | 11/1999 |
| WO | WO 0038754 A | 7/2000 |
| WO | WO 02/26139 A1 | 9/2001 |
| WO | WO 01/87342 A2 | 11/2001 |
| WO | WO 01/87376 A | 11/2001 |
| WO | WO 02/26281 A | 4/2002 |

OTHER PUBLICATIONS

Encyclopedia of Polymer Science and Engineering, vol. 7: fluorocarbon Elastomers, p. 257–267, Mar. 1989.*

Derwent Acc. No. 1999–025723, abstract of DE 19723723 A1, Dec. 3, 1998.*

PCT International Search Report, PCT/US01/30389, Mar. 11, 2002.

European Search Report EP03254747 dated Dec. 3, 2003.

I. Verweire, E. Schact, B. P. Qiang, K. Wang, I. De Scheerder, "Evaluation of Fluorinated Polymers As Coronary Stent Coating," Journal of Materials Science: Materials in Medicine 11. Apr. 2000.

*Primary Examiner*—Ramsey Zacharia

(57) **ABSTRACT**

The present invention includes biocompatible coatings and films for use on implantable medical devices and medical devices containing such coatings and films applied to a surface thereof, which coatings/films are present on the device in an amount effective to provide an inert surface to be in contact with body tissue of a mammal upon implantation of the device in the mammal, and contain a film-forming polyfluoro copolymer containing the polymerized residue of a moiety selected from the group consisting of vinylidenefluoride and tetrafluoroethylene copolymerized with a second moiety other than the first moiety, wherein the relative amounts of the polymerized residue of the first and second moieties are effective to provide the coating and films with properties effective for use in coating implantable med devices.

**5 Claims, 4 Drawing Sheets**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 5,759,205 A | | 6/1998 | Valentini | 623/16 |
| 5,776,184 A | | 7/1998 | Tuch | |
| 5,824,048 A | | 10/1998 | Tuch | |
| 5,824,049 A | | 10/1998 | Ragheb et al. | |
| 5,827,587 A | * | 10/1998 | Fukushi | 428/36.6 |
| 5,865,814 A | | 2/1999 | Tuch | |
| 5,873,904 A | | 2/1999 | Ragheb et al. | |
| 5,879,697 A | | 3/1999 | Ding et al. | |
| 5,897,911 A | | 4/1999 | Loeffler | |
| 5,922,393 A | | 7/1999 | Jayaraman | |
| 5,932,299 A | | 8/1999 | Katoot | |
| 6,153,252 A | | 11/2000 | Hossainy et al. | |

* cited by examiner

FIG. 1

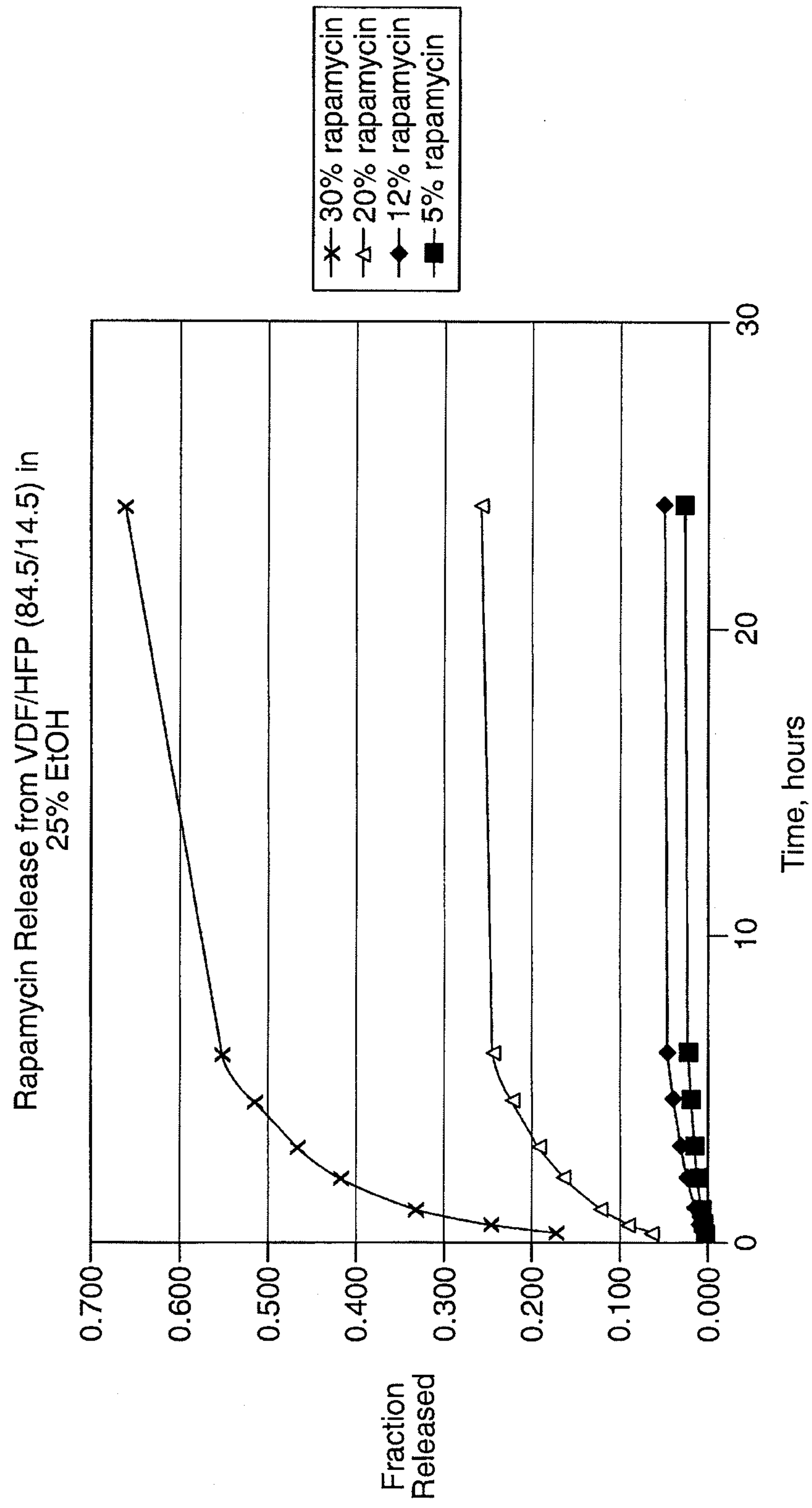

Rapamycin Release from VDF/HFP (84.5/14.5) in 25% EtOH
30% rapamycin
20% rapamycin
12% rapamycin
5% rapamycin
Fraction Released
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
10
20
30
Time, hours

FIG. 2

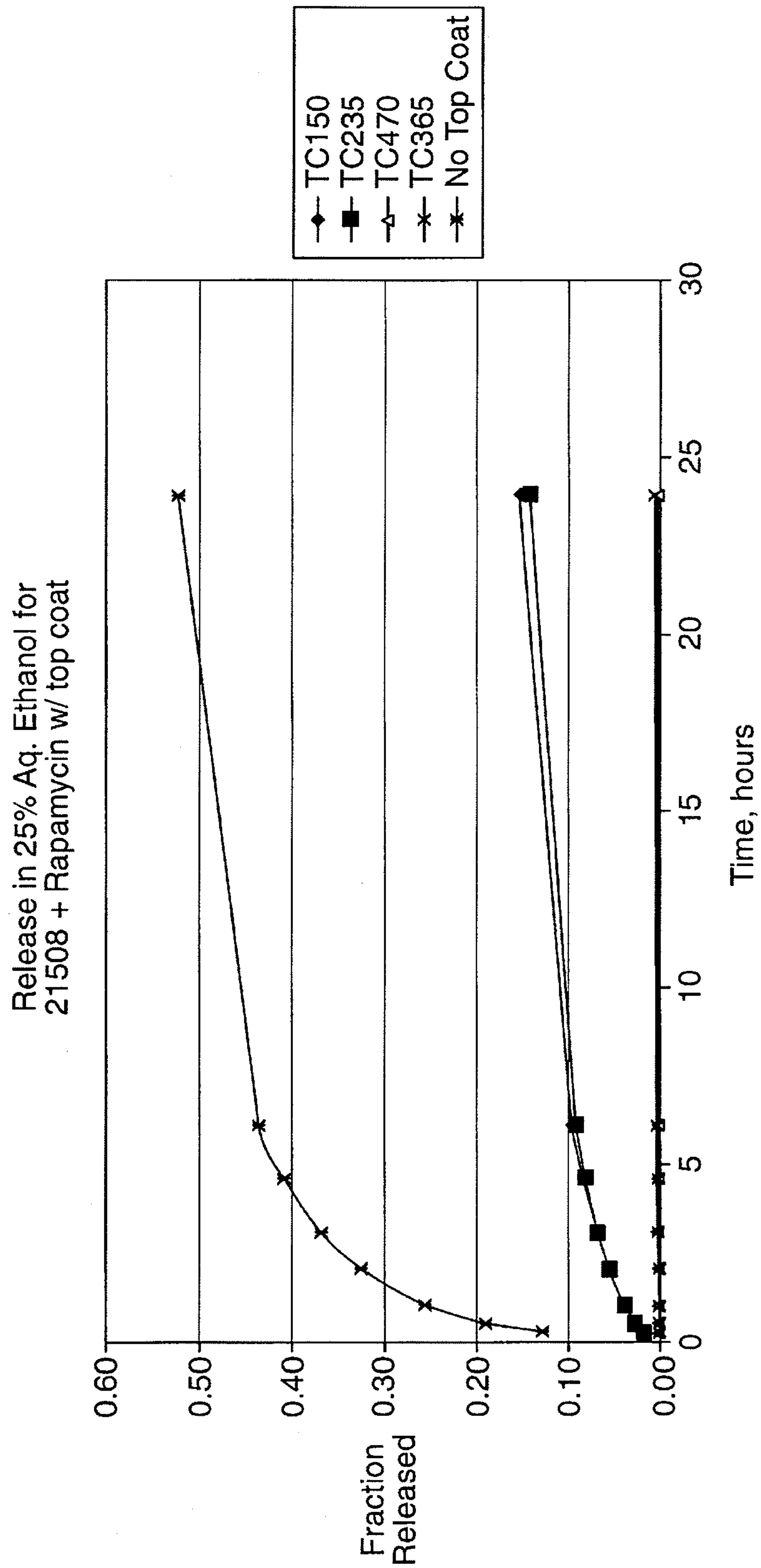

Release in 25% Aq. Ethanol for
21508 + Rapamycin w/ top coat
Fraction
Released
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
5
10
15
20
25
30
Time, hours
TC150
TC235
TC470
TC365
No Top Coat

FIG. 3

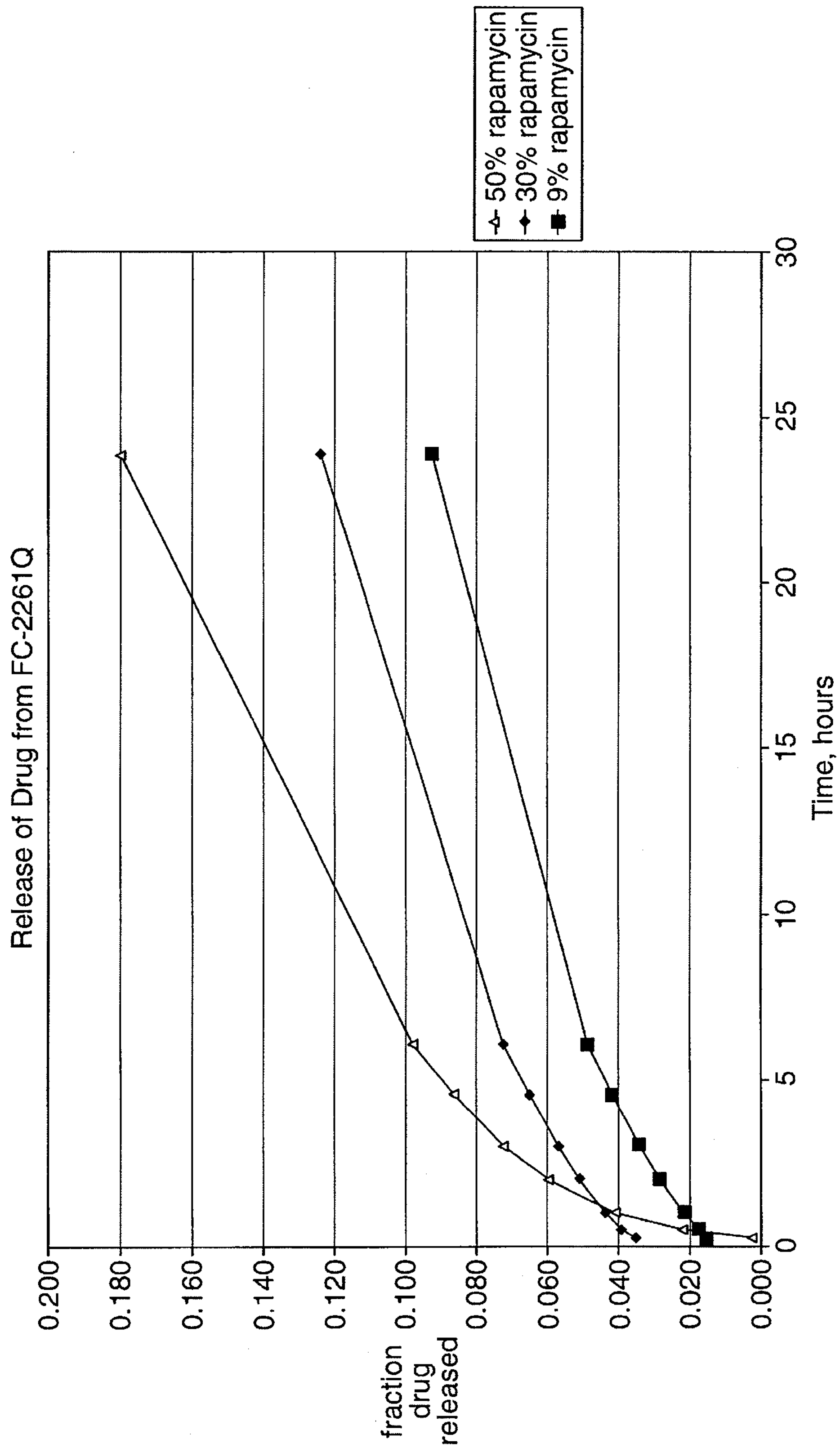
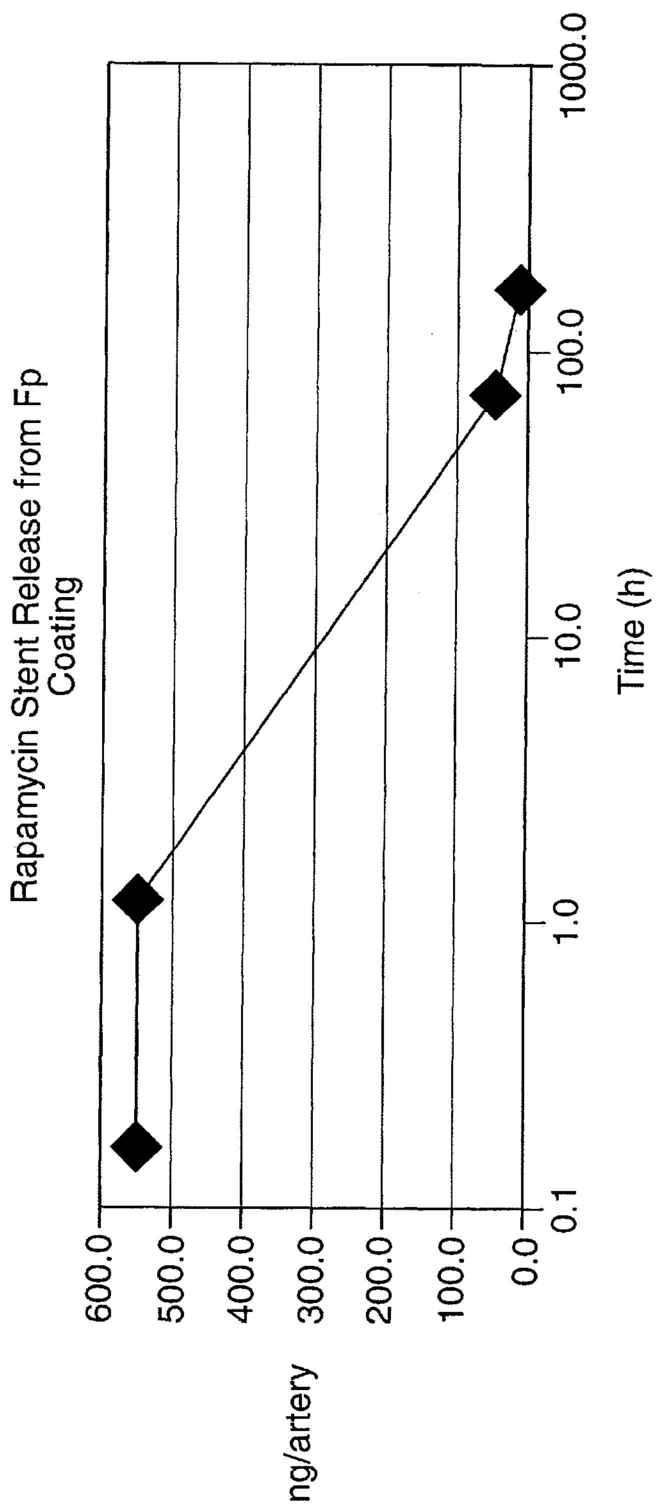

Release of Drug from FC-2261Q
fraction drug released
0.200
0.180
0.160
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0.000
0
5
10
15
20
25
30
Time, hours
50% rapamycin
30% rapamycin
9% rapamycin

*FIG. 4*


Rapamycin Stent Release from Fp Coating
ng/artery
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0.1
1.0
10.0
100.0
1000.0
Time (h)

# COATINGS FOR MEDICAL DEVICES

This patent application is a continuation-in-part of U.S. patent application Ser. No. 09/675,882, filed on Sep. 29,2000, abandoned on Oct. 22, 2002.

## FIELD OF THE INVENTION

The invention relates to the use of polyfluoro copolymers as coatings for implantable surgical medical devices.

## BACKGROUND OF THE INVENTION

Implantable medical devices are used in various medical procedures. Such devices include, without limitation, stents, catheters, sutures, meshes, vascular grafts, shunts and filters for removing emboli.

Stents, which generally are open tubular structures, have become increasingly important in medical procedures to restore the function of body lumens. Stents now are commonly used in translumenial procedures such as angioplasty to restore adequate blood flow to the heart and other organs. However, deployment of stents may stimulate foreign body reactions thereto that result in thrombosis or restenosis.

To avoid these complications, a variety of stent coatings and compositions have been proposed to reduce the incidence of these complications. The coatings may be capable themselves of reducing the stimulus the stent provides to the injured lumen wall, thus reducing the tendency towards thrombosis or restenosis. Alternately, the coating may deliver a pharmaceutical/therapeutic agent or drug to the lumen that reduces smooth muscle tissue proliferation or restenosis. The reported mechanism for delivery of the agent has been via diffusion of the agent through either the bulk polymer, or through pores that are created in the polymer structure, or by erosion of a biodegradable coating.

Both bioabsorbable and biostable compositions have been reported as coatings for stents. They generally have been polymeric coatings that either encapsulate a pharmaceutical/therapeutic agent or drug, e.g. taxol, rapamycin, etc., or bind such an agent to the surface, e.g. heparin-coated stents. These coatings are applied to the stent in a number of ways, including, though not limited to, dip, spray, or spin coating processes.

One class of biostable materials that has been reported as coatings for stents is polyfluoro homopolymers. Polytetrafluoroethylene (PTFE) homopolymers have been used as implants for many years. These homopolymers are not soluble in any solvent at reasonable temperatures and therefore are difficult to coat onto small medical devices while maintaining important features of the devices (e.g. slots in stents).

Stents with coatings made from polyvinylideneflouride homopolymers and containing pharmaceutical/therapeutic agents or drugs for release have been suggested. However, like most crystalline polyfluoro homopolymers, they are difficult to apply as high quality films onto surfaces without subjecting them to relatively high temperatures, e.g. greater than about 125–200° C., that correspond to the melting temperature of the polymer.

It would be advantageous to develop coatings for implantable medical devices that will reduce thrombosis, restenosis, or other adverse reactions, that may include, but do not require, the use of pharmaceutical or therapeutic agents or drugs to achieve such affects, and that possess physical and mechanical properties effective for use in such devices, even when such coated devices are subjected to relatively low maximum temperatures.



## SUMMARY OF THE INVENTION

The present invention includes biocompatible coatings and films for use on implantable medical devices and medical devices comprising such coatings and films applied to a surface thereof that is to be in contact with body tissue of a mammal. The biocompatible film provides an inert surface to be in contact with body tissue of a mammal upon implantation of the device in the mammal. The coating and film comprise a film-forming polyfluoro copolymer comprising the polymerized residue of a first moiety selected from the group consisting of vinylidenefluoride (VDF) and tetrafluoroethylene (TFE), and the polymerized residue of a second moiety other than said first moiety and which is copolymerized with said first moiety, thereby producing the polyflouro copolymer, said second moiety being capable of providing toughness or elastomeric properties to the polyfluoro copolymer, wherein the relative amounts of said polymerized residue of said first moiety and said polymerized residue of said second moiety are effective to provide the coating and film produced therefrom with properties effective for use in coating implantable medical devices.

## BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** indicates the fraction of drug released as a function of time from coatings of the present invention over which no topcoat has been disposed.

FIG. **2** indicates the fraction of drug released as a function of time from coatings of the present invention including a topcoat disposed thereon.

FIG. **3** indicates the fraction of drug released as a function of time from coatings of the present invention over which no topcoat has been disposed.

FIG. **4** indicates in vivo stent release kinetics of rapamycin from poly(VDF/HFP).

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides polymeric coatings comprising a polyfluoro copolymer and implantable medical devices, e.g. stents, coated with a film of the polyfluoro polymeric coating in amounts effective to reduce thrombosis and/or restenosis when such stents are used in, e.g. angioplasty procedures. As used herein, polyfluoro copolymers means those copolymers comprising the polymerized residue of a first moiety selected from the group consisting of vinylidenefluoride and tetrafluoroethylene, the polymerized residue of a second moiety other than the first moiety and which is copolymerized with the first moiety to produce the polyfluoro copolymer, said second moiety being capable of providing toughness or elastomeric properties to the polyfluoro copolymer, wherein the relative amounts of the polymerized residue of the first moiety and the polymerized residue of the second moiety are effective to provide coatings and films made from such polyfluoro copolymers with properties effective for use in coating implantable medical devices.

In certain embodiments, the invention provides an inert, low surface energy coating for medical devices that are implanted into the body of a mammal and later retrieved therefrom. The low surface energy coating makes wetting of the device surface and protein deposition thereon difficult, which could prolong the time for encapsulation in the body, after which time the device could be removed easily.

In certain embodiments of the invention, although not necessary, the coatings may comprise pharmaceutical or

therapeutic agents in amounts effective for achieving desired purposes, e.g. for reducing thrombosis or restenosis, and stents coated with such coatings may provide sustained release of the agents. Films prepared from certain polyfluoro copolymer coatings of the present invention provide the physical and mechanical properties required of conventional coated medical devices, even where maximum temperatures to which the device, coatings and films are exposed are limited to relatively low temperatures, e.g. less than about 100° C., preferably at about ambient temperatures. This is particularly important when using the coating/film to deliver pharmaceutical/therapeutic agent or drugs that are heat sensitive, or when applying the coating onto temperature-sensitive devices such as, but not limited to, catheters. When maximum exposure temperature is not an issue, e.g. where heat-stable agents such as itraconazole are incorporated into the coatings, higher melting thermoplastic polyfluoro copolymers may be used and, if very high elongation and adhesion is required, elastomers may be used. If desired or required, the polyfluoro elastomers may be crosslinked by standard methods described in, e.g. *Modern Fluoropolymers*, J. Shires editor, John Wiley & Sons, New York, 1997, pp. 77–87.

The present invention comprises polyfluoro copolymers that provide improved biocompatible coatings for medical devices. These coatings provide inert surfaces to be in contact with body tissue of a mammal, e.g. a human, sufficient to reduce thrombosis, or restenosis, or other undesirable reactions. While most reported coatings made from polyfluoro homopolymers are insoluble and/or require high heat, e.g. greater than about 125° C., to obtain films with adequate physical and mechanical properties for use on implantable devices, e.g. stents, or are not particularly tough or elastomeric, films prepared from the polyfluoro copolymer coatings of the present invention provide adequate adhesion, toughness or elasticity, and resistance to cracking when formed on medical devices claimed herein. In certain embodiments, this is the case even where the coated devices are subjected to relatively low maximum temperatures, e.g. less than about 100° C., preferably less than about 65° C., and more preferably about 60° C. or less. In such cases, preferred polyfluoro copolymers may comprise the polymerized residue of from about 65 to about 55 weight percent polymerized residue of the first moiety, e.g. VDF, and from about 35 to about 45 weight percent polymerized residue of the second moiety, e.g. hexafluoropropylene. In certain embodiments, such polyfluoro copolymers will be crystalline, although amorphous copolymers of similar composition also are employed.

The polyfluoro copolymers used for coatings according to the present invention must be film-forming polymers that have molecular weight high enough so as not to be waxy or tacky. The polymers and films formed therefrom must adhere to the stent and not be readily deformable after deposition on the stent as to be able to be displaced by hemodynamic stresses. The polymer molecular weight must be high enough to provide sufficient toughness so that films comprising the polymers will not be rubbed off during handling or deployment of the stent. In certain embodiments the coating will not crack where expansion of the stent or other medical devices, such as vena cava filters, occurs. The flow point of the polymer used in the present invention should be above 40° C., preferably above about 45° C., more preferably above 50° C. and most preferably above 55° C.

Coatings of the present invention comprise polyfluoro copolymers, as defined hereinabove. The second moiety copolymerized with the first moiety to prepare the polyfluoro copolymer may be selected from those biocompatible monomers that would provide biocompatible polymers acceptable for implantation in a mammal, while maintaining sufficient elastomeric film properties for use on medical devices claimed herein. Such monomers include, without limitation, hexafluoropropylene (HFP), tetrafluoroethylene (TFE), VDF, 1-hydropentafluoropropylene, perfluoro (methyl vinyl ether), chlorotrifluoroethylene (CTFE), pentafluoropropene, trifluoroethylene, hexafluoroacetone and hexafluoroisobutylene.

Polyfluoro copolymers used in the present invention typically comprise vinylidinefluoride copolymerized with HFP, in the weight ratio of from about 50 to about 92 weight percent vinylidinefluoride to about 50 to about 8 weight percent HFP. Preferably, polyfluoro copolymers used in the present invention comprise from about 50 to about 85 weight percent VDF copolymerized with from about 50 to about 15 weight percent HFP. More preferably, the polyfluoro copolymers will comprise from about 55 to about 70 weight percent VDF copolymerized with from about 45 to about 30 weight percent HFP. Even more preferably, polyfluoro copolymers comprise from about 55 to about 65 weight percent VDF copolymerized with from about 45 to about 35 weight percent HFP. Such polyfluoro copolymers are soluble, in varying degrees, in solvents such as dimethylacetamide (DMAc), tetrahydrofuran, dimethyl formamide, dimethyl sulfoxide and n-methyl pyrrolidone. Some are soluble in methylethylketone (MEK), acetone, methanol and other solvents commonly used in applying coatings to conventional implantable medical devices.

Conventional polyfluoro homopolymers are crystalline and difficult to apply as high quality films onto metal surfaces without exposing the coatings to relatively high temperatures that correspond to the melting temperature (Tm) of the polymer. The elevated temperature serves to provide films prepared from such PVDF homopolymer coatings that exhibit sufficient adhesion of the film to the device, while preferably maintaining sufficient flexability to resist film cracking upon expansion/contraction of the coated medical device. Certain films and coatings according to the present invention provide these same physical and mechanical properties, or essentially the same properties, even when the maximum temperatures to which the coatings and films are exposed is less than about 100° C., and preferably less than about 65° C. This is particularly important when the coatings/films comprise pharmaceutical or therapeutic agents or drugs that are heat sensitive, e.g. subject to chemical or physical degradation or other heat-induced negative affects, or when coating heat sensitive substrates of medical devices, e.g. subject to heat-induced compositional or structural degradation.

Depending on the particular device upon which the coatings and films of the present invention are to be applied and the particular use/result required of the device, polyfluoro copolymers used to prepare such devices may be crystalline, semi-crystalline or amorphous.

Where devices have no restrictions or limitations with respect to exposure of same to elevated temperatures, e.g. 100° C. or higher, crystalline polyfluoro copolymers may be employed. Crystalline polyfluoro copolymers tend to resist the tendency to flow under applied stress or gravity when exposed to temperatures above their glass transition (Tg) temperatures. Crystalline polyfluoro copolymers provide tougher coatings and films than their fully amorphous counterparts. In addition, crystalline polymers are more lubricious and more easily handled through crimping and transfer processes used to mount self-expanding stents, e.g. nitinol stents.

Semi-crystalline and amorphous polyfluoro copolymers are advantageous where exposure to elevated temperatures is an issue, e.g. where heat-sensitive pharmaceutical or therapeutic agents are incorporated into the coatings and films, or where device design, structure and/or use preclude exposure to such elevated temperatures. Semi-crystalline polyfluoro copolymer elastomers comprising relatively high levels, e.g. from about 30 to about 45 weight percent of the second moiety, e.g. HFP, copolymerized with the first moiety, e.g. VDF, have the advantage of reduced coefficient of friction and self-blocking relative to amorphous polyfluoro copolymer elastomers. Such characteristics can be of significant value when processing, packaging and delivering medical devices coated with such polyfluoro copolymers. In addition, such polyfluoro copolymer elastomers comprising such relatively high content of the second moiety serves to control the solubility of certain agents, e.g. Sirolimus, in the polymer and therefore controls permeability of the agent through the matrix.

Polyfluoro copolymers utilized in the present inventions may be prepared by various known polymerization methods. For example, high pressure, free-radical, semi-continuous emulsion polymerization techniques such as those disclosed in *Fluoroelastomers-dependence of relaxation phenomena on composition*, POLYMER 30, 2180, 1989, by Ajroldi, et al, may be employed to prepare amorphous polyfluoro copolymers, some of which may be elastomers. In addition, free-radical batch emulsion polymerization techniques disclosed herein may be used to obtain polymers that are semi-crystalline, even where relatively high levels of the second moiety, e.g. greater than about 19–20 mole percent (equivalent to about 36–37 weight percent), are included.

One embodiment of the invention comprises stents coated with a film of a polyfluoro copolymer according to the present invention. Conventional stents are used in transluminal procedures such as angioplasty to restore adequate blood flow to the heart and other organs. They generally are cylindrical and perforated with passages that are slots, ovoid, circular or the like shape. Stents also may be composed of helically wound or serpentine wire structures in which the spaces between the wires form passages. Stents may be flat perforated structures that are subsequently rolled to form tubular or cylindrical structures that are woven, wrapped, drilled, etched or cut to form passages. Examples of stents that may be advantageously coated by polyfluoro copolymers of the present invention include, but are not limited to, stents described in U.S. Pat. Nos. 4,733,665; 4,800,882; 4,886,062, 5,514,154, and 6,190,403, the contents each of which is incorporated herein in its entirety as if set forth herein. These stents can be made of biocompatible materials, including biostable and bioabsorbable materials. Suitable biocompatible metals include, but are not limited to, stainless steel, tantalum, titanium alloys (including nitinol), and cobalt alloys (including cobalt-chromium-nickel alloys). Suitable nonmetallic biocompatible materials include, but are not limited to, polyamides, polyolefins (i.e. polypropylene, polyethylene etc.), nonabsorbable polyesters (i.e. polyethylene terephthalate), and bioabsorbable aliphatic polyesters (i.e. homopolymers and copolymers of lactic acid, glycolic acid, lactide, glycolide, para-dioxanone, trimethylene carbonate, ε-caprolactone, and blends thereof).

The film-forming biocompatible polymer coatings generally are applied to the stent in order to reduce local turbulence in blood flow through the stent, as well as adverse tissue reactions. The coatings and films formed therefrom also may be used to administer a pharmaceutically active material to the site of the stent placement. Generally, the amount of polymer coating to be applied to the stent will vary depending on, among other possible parameters, the particular polyfluoro copolymer used to prepare the coating, the stent design and the desired effect of the coating. Generally, the coated stent will comprise from about 0.1 to about 15 weight percent of the coating, preferably from about 0.4 to about 10 weight percent. The polyfluoro copolymer coatings may be applied in one or more coating steps, depending on the amount of polyfluoro copolymer to be applied. Different polyfluoro copolymers may be used for different layers in the stent coating. In fact, in certain embodiments, it is highly advantageous to use a diluted first coating solution comprising a polyfluoro copolymer as a primer to promote adhesion of a subsequent polyfluoro copolymer coating layer that may contain pharmaceutically active materials. The individual coatings may be prepared from different polyfluoro copolymers.

Additionally, a top coating can be applied to delay release of the pharmaceutical agent, or they could be used as the matrix for the delivery of a different pharmaceutically active material. Layering of coatings can be used to stage release of the drug or to control release of different agents placed in different layers.

Blends of polyfluoro copolymers also may be used to control the release rate of different agents or to provide desirable balance of coating properties, i.e. elasticity, toughness, etc., and drug delivery characteristics, e.g. release profile. Polyfluoro copolymers with different solubilities in solvents can be used to build up different polymer layers that may be used to deliver different drugs or to control the release profile of a drug. For example, polyfluoro copolymers comprising 85.5/14.5 (wt/wt) of poly(VDF/HFP) and 60.6/39.4 (wt/wt) of poly(VDF/HFP) are both soluble in DMAc. However, only the 60.6/39.4 poly(VDF/HFP) polyfluoro copolymer is soluble in methanol.

So, a first layer of the 85.5/14.5 poly(VDF/HFP) polyfluoro copolymer comprising a drug could be over-coated with a topcoat of the 60.6/39.4 poly(VDF/HFP) polyfluoro copolymer made with the methanol solvent. The top coating can be used to delay the drug deliver of the drug contained in the first layer. Alternatively, the second layer could contain a different drug to provide for sequential drug delivery. Multiple layers of different drugs could be provided by alternating layers of first one polyfluoro copolymer, then the other. As will be readily appreciated by those skilled in the art numerous layering approaches can be used to provide the desired drug delivery.

The coatings can be used to deliver therapeutic and pharmaceutic agents such as, but not limited to: antiproliferative/antimitotic agents including natural products such as vinca alkaloids (i.e. vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (i.e. etoposide, teniposide), antibiotics (dactinomycin (actinomycin D) daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which don't have the capacity to synthesize their own asparagine); antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nirtosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes—dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs

(fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine{cladribine}); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (i.e. estrogen); Anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory; antisecretory (breveldin); antiinflammatory: such as adrenocortical steroids (cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6α-methylprednisolone, triamcinolone, betamethasone, and dexamethasone), non-steroidal agents (salicylic acid derivatives i.e. aspirin; para-aminophenol derivatives i.e. acetominophen; Indole and indene acetic acids (indomethacin, sulindac, and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate); immunosuppressives: (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); Angiogenic agents: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); nitric oxide donors; cell cycle inhibitors; mTOR inhibitors; growth factor signal transduction knase inhibitors; anti-sense oligonucleotide; prodrug molecules; and combinations thereof.

Coatings may be formulated by mixing one or more therapeutic agents with the coating polyfluoro copolymers in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the coating mixture may include one or more additives, e.g., nontoxic auxiliary substances such as diluents, carriers, excipients, stabilizers or the like. Other suitable additives may be formulated with the polymer and pharmaceutically active agent or compound. For example, a hydrophilic polymer may be added to a biocompatible hydrophobic coating to modify the release profile, or a hydrophobic polymer may be added to a hydrophilic coating to modify the release profile. One example would be adding a hydrophilic polymer selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxylmethyl cellulose, and hydroxymethyl cellulose to a polyfluoro copolymer coating to modify the release profile. Appropriate relative amounts can be determined by monitoring the in vitro and/or in vivo release profiles for the therapeutic agents.

The best conditions for the coating application are when the polyfluoro copolymer and pharmaceutic agent have a common solvent. This provides a wet coating that is a true solution. Less desirable, yet still usable, are coatings that contain the pharmaceutical agent as a solid dispersion in a solution of the polymer in solvent. Under the dispersion conditions, care must be taken to ensure that the particle size of the dispersed pharmaceutical powder, both the primary powder size and its aggregates and agglomerates, is small enough not to cause an irregular coating surface or to clog the slots of the stent that need to remain essentially free of coating. In cases where a dispersion is applied to the stent and the smoothness of the coating film surface requires improvement, or to be ensured that all particles of the drug are fully encapsulated in the polymer, or in cases where the release rate of the drug is to be slowed, a clear (polyfluoro copolymer only) topcoat of the same polyfluoro copolymer used to provide sustained release of the drug or another polyfluoro copolymer that further restricts the diffusion of the drug out of the coating can be applied. The topcoat can be applied by dip coating with mandrel to clear the slots, referred to herein as the dip and wipe method. This method is disclosed in U.S. Pat. No. 6,153,252, the contents of which are incorporated herein in their entirety. Other methods for applying the topcoat include spin coating and spray coating. Dip coating of the top coat can be problematic if the drug is very soluble in the coating solvent, which swells the polyfluoro copolymer, and the clear coating solution acts as a zero concentration sink and redissolves previously deposited drug. The time spent in the dip bath may need to be limited so that the drug is not extracted out into the drug-free bath. Drying should be rapid so that the previously deposited drug does not completely diffuse into the topcoat.

The amount of therapeutic agent will be dependent upon the particular drug employed and medical condition being treated. Typically, the amount of drug represents about 0.001% to about 70%, more typically about 0.001% to about 60%.

The quantity and type of polyfluoro copolymers employed in the coating film containing the pharmaceutic agent will vary depending on the release profile desired and the amount of drug employed. The product may contain blends of the same or different polyfluoro copolymers having different molecular weights to provide the desired release profile or consistency to a given formulation.

Polyfluoro copolymers may release dispersed drug by diffusion. This can result in prolonged delivery (over, say 1 to 2,000 hours, preferably 2 to 800 hours) of effective amounts (say, 0.001 $\mu g/cm^2$-min to 100 $\mu g/cm^2$-min) of the drug. The dosage can be tailored to the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like. Individual formulations of drugs and polyfluoro copolymers may be tested in appropriate in vitro and in vivo models to achieve the desired drug release profiles. For example, a drug could be formulated with a polyfluoro copolymer, or blend of polyfluoro copolymers, coated onto a stent and placed in an agitated or circulating fluid system, e.g. 25% ethanol in water. Samples of the circulating fluid could be taken to determine the release profile (such as by HPLC, UV analysis or use of radiotagged molecules). The release of a pharmaceutical compound from a stent coating into the interior wall of a lumen could be modeled in appropriate animal system. The drug release profile could then be monitored by appropriate means such as, by taking samples at specific times and assaying the samples for drug concentration (using HPLC to detect drug concentration). Thrombus formation can be modeled in animal models using the $^{111}$In-platelet imaging methods described by Hanson and Harker, Proc. Natl. Acad. Sci. USA 85:3184–3188 (1988). Following this or similar procedures, those skilled in the art will be able to formulate a variety of stent coating formulations.

While not a requirement of the present invention, the coatings and films may be crosslinked once applied to the medical devices. Crosslinking may be affected by any of the known crosslinking mechanisms, such as chemical, heat or light. In addition, crosslinking initiators and promoters may be used where applicable and appropriate. In those embodiments utilizing crosslinked films comprising pharmaceutical agents, curing may affect the rate at which the drug diffuses from the coating. Crosslinked polyfluoro copolymers films and coatings of the present invention also may be used without drug to modify the surface of implantable medical devices.

## EXAMPLES

### Example 1

A poly(VDF) homopolymer (Solef 1008 from Solvay Advanced Polymers, Houston, Tex., Tm about 175° C.) and polyfluoro copolymers of poly(VDF/HFP), 92/8 and 91/9 weight percent VDF/HFP, respectively, as determined by $F^{19}$ NMR (eg: Solef 11010 and 11008, Solvay Advanced Polymers, Houston, Tex., Tm about 159° C. and 160° C., respectively) were examined as potential coatings for stents. These polymers are soluble in solvents such as, but not limited to, DMAc, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), tetrahydrofuran (THF) and acetone. Polymer coatings were prepared by dissolving the polymers in acetone, at 5 weight percent as a primer, or by dissolving the polymer in 50/50 DMAc/acetone, at 30 weight percent as a topcoat. Coatings that were applied to the stents by dipping and dried at 60° C. in air for several hours, followed by 60° C. for 3 hours in a <100 mm Hg vacuum, resulted in white foamy films. As applied, these films adhered poorly to the stent and flaked off, indicating they were too brittle. When stents coated in this manner were heated above 175° C., i.e. above the melting temperature of the polymer, a clear, adherent film was formed. Such coatings require high temperatures, e.g. above the melting temperature of the polymer, to achieve high quality films.

### Example 2

A polyfluoro copolymer (Solef 21508) comprising 85.5 weight percent VDF copolymerized with 14.5 weight percent HFP, as determined by $F^{19}$ NMR, was evaluated. This copolymer is less crystalline than the polyfluoro homopolymer and copolymers described in Example 1. It also has a lower melting point reported to be about 133° C. Once again, a coating comprising about 20 weight percent of the polyfluoro copolymer was applied from a polymer solution in 50/50 DMAc/MEK. After drying (in air) at 60° C. for several hours, followed by 60° C. for 3 hours in a <100 mtorr Hg vacuum, clear adherent films were obtained. This eliminated the need for a high temperature heat treatment to achieve high quality films. Coatings were smoother and more adherent than those of Example 1. Some coated stents that underwent expansion show some degree of adhesion loss and "tenting" as the film pulls away from the metal. Where necessary, modification of coatings containing such copolymers may be made, e.g. by addition of plasticizers or the like to the coating compositions. Films prepared from such coatings may be used to coat stents or other medical devices, particularly where those devices are not susceptible to expansion to the degree of the stents.

The coating process above was repeated, this time with a coating comprising the 85.5/14.6 (wt/wt) (VDF/HFP) and about thirty (30) weight percent of rapamycin (Wyeth-Ayerst Laboratories, Philadelphia, Pa.), based on total weight of coating solids. Clear films that would occasionally crack or peel upon expansion of the coated stents resulted. It is believed that inclusion of plasticizers and the like in the coating composition will result in coatings and films for use on stents and other medical devices that are not susceptible to such cracking and peeling.

### Example 3

Polyfluoro copolymers of still higher HFP content then were examined. This series of polymers were not semicrystalline, but rather are marketed as elastomers. One such



copolymer is Fluorel FC-2261Q (from Dyneon, a 3M-Hoechst Enterprise, Oakdale, Minn.), a 60.6/39.4 (wt/wt) copolymer of VDF/HFP. Although this copolymer has a Tg well below room temperature (Tg about −20° C.), it is not tacky at room temperature or even at 60° C. This polymer has no detectable crystallinity when measured by Differential Scanning Calorimetry (DSC) or by wide angle X-ray diffraction. Films formed on stents as described above were non-tacky, clear, and expanded without incident when the stents were expanded.

The coating process above was repeated, this time with coatings comprising the 60.6/39.4 (wt/wt) poly(VDF/HFP) and about nine (9), thirty (30) and fifty (50) weight percent of rapamycin , based on total weight of coating solids, respectively. Coatings comprising about 9 and 30 weight percent rapamycin provided white, adherent, tough films that expanded without incident on the stent. Inclusion of 50% drug, in the same manner, resulted in some loss of adhesion upon expansion.

Changes in the comonomer composition of the polyfluoro copolymer also can affect the nature of the solid state coating, once dried. For example, the semi-crystalline copolymer, Solef 21508, containing 85.5% VDF polymerized with 14.5% by weight HFP forms homogeneous solutions with about 30% rapamycin (drug weight divided by total solids weight, e.g. drug plus copolymer) in DMAc and 50/50 DMAc/MEK. When the film is dried (60° C./16 hours followed by 60° C./3 hours in vacuum of 100 mm Hg) a clear coating, indicating a solid solution of the drug in the polymer, is obtained. Conversely, when an amorphous copolymer, Fluorel FC-2261Q, of poly(VDF/HFP) at 60.6/39.5 (wt/wt) forms a similar 30% solution of rapamycin in DMAc/MEK and is similarly dried, a white film, indicating phase separation of the drug and the polymer, is obtained. This second drug containing film is much slower to release the drug into an in vitro test solution of 25% ethanol in water than is the former clear film of crystalline Solef 21508. X-ray analysis of both films indicates that the drug is present in a non-crystalline form. Poor or very low solubility of the drug in the high HFP-containing copolymer results in slow permeation of the drug through the thin coating film. Permeability is the product of diffusion rate of the diffusing species (in this case the drug) through the film (the copolymer) and the solubility of the drug in the film.

### Example 4

In Vitro Release Results of Rapamycin from Coating

FIG. 1 is a plot of data for the 85.5/14.5 VDF/HFP polyfluoro copolymer, indicating fraction of drug released as a function of time, with no topcoat. FIG. 2 is a plot of data for the same polyfluoro copolymer over which a topcoat has been disposed, indicating that most effect on release rate is with a clear topcoat. As shown therein, TC150 refers to a device comprising 150 micrograms of topcoat, TC235 refers to 235 micrograms of topcoat, etc. The stents before top coating had an average of 750 micrograms of coating containing 30% rapamycin (based on drug/[drug+polymer]) FIG. 3 is a plot for the 60.6/39.4 VDF/HFP polyfluoro copolymer, indicating fraction of drug released as a function of time, showing significant control of release rate from the coating without the use of a topcoat. Release is controlled by loading of drug in the film.

### Example 5

In Vivo Stent Release Kinetics of Rapamycin from Poly (VDF/HFP)

Nine (9) New Zealand white rabbits (2.5–3.0 kg) on a normal diet were given aspirin 24 hours prior to surgery,

again just prior to surgery and for the remainder of the study. At the time of surgery, animals were premedicated with Acepromazine (0.1–0.2 mg/kg) and anesthetized with a Ketamine/Xylazine mixture (40 mg/kg and 5 mg/kg, respectively). Animals were given a single intraprocedural dose of heparin (150 IU/kg, i.v.).

Arteriectomy of the right common carotid artery was performed and 5 F catheter introducer (Cordis, Inc.) placed in the vessel and anchored with ligatures. Iodine contrast agent was injected to visualize the right common carotid artery, brachlocephalic trunk and aortic arch. A steerable guide wire (0.014 inch/180 cm, Cordis, Inc.) was inserted via the introducer and advanced sequentially into each iliac artery to a location where the artery possesses a diameter closest to 2 mm using the angiographic mapping done previously. Two stents coated with a film made from poly (VDF/HFP):(60.6/39.4), with about 30% rapamycin(based on drug/[drug+polymer]) were deployed in each animal where feasible, one in each iliac artery, using 3.0 mm balloon and inflation to 8–10 ATM for 30 seconds followed after a 1 minute interval by a second inflation to 8–10 ATM for 30 seconds. Follow-up angiographs visualizing both iliac arteries are obtained to confirm correct deployment position of the stent.

At the end of procedure, the carotid artery was ligated and the skin is closed with 3/0 vicryl suture using a one layered interrupted closure. Animals were given butoropanol (0.4 mg/kg, s.c.) and gentamycin (4 mg/kg, i.m.). Following recovery, the animals were returned to their cages and allowed free access to food and water.

Due to early deaths and surgical difficulties, 2 animals were not used in this analysis. Stented vessels were removed from the remaining 7 animals at the following time points: 1 vessel (1 animal) at 10 min post implant; 6 vessels (3 animals) between 45 min and 2 h post-implant (average, 1.2 hours); 2 vessels (2 animals) at 3 d post implant; and 2 vessels (1 animal) at 7 d post-implant. In one animal at 2 hours, the stent was retrieved from the aorta rather than the iliac artery. Upon removal, arteries were carefully trimmed at both the proximal and distal ends of the stent. Vessels were then carefully dissected free of the stent, flushed to remove any residual blood, and both stent and vessel frozen immediately, wrapped separately in foil, labeled and kept frozen at −80° C. When all samples had been collected, vessels and stents were frozen, transported and subsequently analyzed for rapamycin in tissue. Results are shown in FIG. 4.

## Example 6

Purifying the Polymer

The Fluorel FC-2261Q copolymer was dissolved in MEK at about 10 weight percent and was washed in a 50/50 mixture of ethanol/water. The (ethanol/water): MEK solution ratio=about 14:1. The polymer precipitated out and was separated from the solvent phase by centrifugation. The polymer again was dissolved in MEK and the washing procedure repeated. The polymer was dried after each washing step at 60° C. in a vacuum oven (<200 mtorr) over night.

## Example 7

In Vivo Testing of Coated Stents in Porcine Coronary Arteries

CrossFlex® stents (available from Cordis, a Johnson & Johnson Company) were coated with the "as received" Fluorel FC-2261Q PVDF copolymer and with the purified polyfluoro copolymer of example 6, using the dip and wipe approach. The coated stents were sterilized using ethylene oxide and a standard cycle. The coated stents and bare metal stents (controls) were implanted in porcine coronary arteries, where they remained for 28 days.

Angiography was performed on the pigs at implantation and at 28 days. Angiography indicated that the control uncoated stent exhibited about 21 percent restenosis. The polyfluoro copolymer "as received" exhibited about 26% restenosis (equivalent to the control) and the washed copolymer exhibited about 12.5% restenosis.

Histology results reported neointimal area at 28 days to be 2.89±0.2, 3.57±0.4 and 2.75±0.3, respectively, for the bare metal control, the unpurified copolymer and the purified copolymer.

## Example 8

Utilizing the following high pressure, free-radical batch emulsion polymerization technique, a series of semi-crystalline, poly(VDF/HFP) copolymer elastomers was prepared.

The VDF and HFP monomers were premixed under pressure in a pressure vessel. HPLC-grade water, surfactant and initiator were mixed outside of a 2 liter Zipperclave® reactor (Autoclave Engineers, Erie, Pa.) and then charged to the reactor, which then was sealed. The premixed monomers then were transferred under nitrogen pressure to the reactor. While stirring, the reactor was raised to the desired temperature and held for a predetermined period of time. The reactor then was cooled and residual monomer vented. The resultant polymer latex was removed from the reactor and coagulated or crashed by adding dilute hydrochloric acid, followed by aqueous sodium chloride. The resulting polymer was washed extensively with water and dried.

The polyfluoro copolymers then were compared with respect to kinetic coefficient of friction of a film prepared therefrom to the kinetic coefficient of friction of a film prepared from a commercial amorphous polyfluoro copolymer comprising 59.5 weight percent VDF copolymerized with 40.5 weight percent HFP utilizing the following procedure.

A 57.2 mm wide by 140.0 mm long polymer film was cast on a 101.6 mm wide by 203.2 mm long aluminum panel (Q-panel, anodized finish, A-48). A silicone rubber gasket was placed on the aluminum panel and clamped using binder clips. The mold was leveled in a fume hood using a bubble level. Approximate 5.0 g of 10.0% polymer solution in methyl ethyl ketone was poured into the mold slowly. The film was dried at room temperature for 3 days followed by 3 hours at 23° C. and 50% R.H. prior to testing.

The kinetic coefficient of friction of the polymer film was measured in accordance with the method described in ASTM D 1894-00, "Static and Kinetic Coefficients of Friction of Plastic Film and Sheeting", Method C. A 46.5 g Teflon block, 25.4 mm wide by 41.3 mm long by 19.1 mm thick, with an eye screw fastened in one end was used as a sled. The surface of the sled that contacted to the film was polished using 500-grit sandpaper. The Teflon sled was attached to a flexible beaded chain and pulled using an Instron tensile tester at a rate of 150 mm/min., at 23° C. and 50% R.H. Five measurements was made on each film sample. The thickness of the film was measured using a digital thickness gauge. The kinetic coefficient test results are given in Table I. The maximum kinetic coefficient of friction of five measurements of each film were averaged and reported.

The Differential Scanning Calorimetry (DSC) data were obtained on the following polymers using vacuum dried

films in a TA Instruments Model 2920 Modulated DSC in standard (non-modulated) DSC mode. The samples were quenched to −80° C. and heated at 10° C./min to 275° C. in nitrogen. The data are reported as ΔH (J/g) for endothermic, melting events above glass transition temperature (Tg).

TABLE I

Kinetic Coefficient of Polymer Film

| Sample I.D. Wt/wt VDF/HFP | Film Thickness ($\mu$m) | Max. Kinetic Coefficient | DSC ΔH (J/g) |
|---|---|---|---|
| Commercial 59.5/40.5 | 22.9 | 2.65 $\sigma = 0.17$ | None |
| Polymer 8a 55.1/44.9 | 38.6 | 1.71 $\sigma = 0.09$ | 16.5 |
| Polymer 8b 56.8/43.2 | 27.5 | 0.27 $\sigma = 0.03$ | 15 |
| Polymer 8c 68.3/31.7 | 25.4 | 0.35 $\sigma = 0.07$ | 19.5 |
| Polymer 8d 59.9/40.1 | 21.1 | 2.12 $\sigma = 0.04$ | 4.5 |

What is claimed is:

**1**. An implantable medical device: comprising,

a biocompatible film effective to provide an inert surface to be in contact with body tissue of a mammal upon implantation of said device in said mammal, said film comprising a polyfluoro copolymer comprising from about 50 to about 92 weight percent of polymerized residue of vinylidenefluoride and about 50 to about 8 weight percent of polymerized residue of hexafluoropropylene.



**2**. The device of claim **1**, wherein said polyfluoro copolymer comprises from about 50 to about 85 weight percent of said polymerized residue of said vinylidenefluoride copolymerized with from about 50 to about 15 weight percent of said polymerized residue of said hexafluoropropylene.

**3**. The device of claim **1**, wherein said copolymer comprises from about 55 to about 65 weight percent of said polymerized residue of said vinylidenefluoride copolymerized with from about 45 to about 35 weight percent of said polymerized residue of said hexafluoropropylene.

**4**. The implantable medical device of claim **1**, wherein said film further comprises effective amounts of a therapeutic and/or pharmaceutical agent.

**5**. The implantable device of claim **1** wherein said polyfluoro copolymer is effective to provide said film with properties effective for use in coating said implantable medical device when said coated device is subjected to a maximum temperature of less than 100° C.

* * * * *

# A3896-3909

# REDACTED

## CERTIFICATE OF SERVICE

I hereby certify that on the 19th day of October, 2009, the attached **REDACTED PUBLIC VERSION OF APPENDIX OF EXHIBITS TO DEFENDANTS/COUNTER-PLAINTIFFS JOHNSON & JOHNSON AND CORDIS'S OPPOSITION TO PLAINITFFS' MOTIONS FOR SUMMARY JUDGMENT OF INVALIDITY PURSUANT TO 35 U.S.C. § 103** was served upon counsel of record at the address and in the manner indicated:

| | |
|---|---|
| Josy W. Ingersoll, Esquire<br>Young Conaway Stargatt & Taylor<br>The Brandywine Building<br>1000 West Street<br>Wilmington, DE 19801 | VIA ELECTRONIC MAIL |
| Richard L. DeLucia, Esquire<br>Kenyon & Kenyon<br>One Broadway<br>New York, NY 10004 | VIA ELECTRONIC MAIL |
| Nicholas J. Nowak, Esquire<br>Kenyon & Kenyon<br>1500 K Street N.W., Suite 700<br>Washington, DC 20036 | VIA ELECTRONIC MAIL |
| James F. Hibey, Esquire<br>Howrey LLP<br>1299 Pennsylvania Ave., NW<br>Washington, DC 20004 | VIA ELECTRONIC MAIL |
| Robert E. McAlhany, Jr., Esquire<br>Howrey LLP<br>1950 University Avenue, 4th Floor<br>East Palo Alto, CA 94303 | VIA ELECTRONIC MAIL |

Kate Berezutskaya, Esquire
Howrey LLP
321 North Clark Street
Suite 3400
Chicago, IL 60654

VIA ELECTRONIC MAIL

*/s/ John G. Day*

John G. Day